THE AMERICAN JOURNAL OF ROENTGENOLOGY
RADIUM THERAPY AND NUCLEAR MEDICINE

VOL. 78 SEPTEMBER, 1957 No. 3

COOLEY'S ANEMIA: A REVIEW OF THE ROENTGENOGRAPHIC FINDINGS IN THE SKELETON*

HICKEY LECTURE, 1957

By JOHN CAFFEY, M.D.
NEW YORK, NEW YORK

IT IS a high privilege, indeed, to honor Preston M. Hickey in this lecture—Hickey, the outstanding pioneer radiologist of Michigan and one of the great figures of early American radiology. It was my good fortune to meet this kindly and gracious physician on two occasions; and to enjoy the friendly courtesies with which he greeted younger colleagues to his clinic. A review of Dr. Hickey's accomplishments would be superfluous for this audience, which includes many who knew him intimately and some who are his immediate professional heirs. Personally, I cherish what I believe to be a unique distinction. Dr. Hickey's predecessor, James G. Van Zwaluwenburg, first Professor of Radiology at the University of Michigan, was my first teacher of radiology; and Dr. Hickey's successor at the University of Michigan and current Professor of Radiology at Ann Arbor, Fred Jenner Hodges, has been a valued friend for almost forty years, since our days as residents in internal medicine at Barnes Hospital in St. Louis.

My subject, Cooley's anemia, seems especially appropriate for this occasion because the recognition of this disease was an exclusively Michigan contribution, and a major one in both radiology and pediatrics. It is also a happy coincidence that Dr. Hickey and Dr. Thomas B. Cooley were for many years colleagues on the Medical Faculty of Wayne University. In many ways Cooley, a pioneer pediatrician of Michigan, was the counterpart of Hickey, the pioneer radiologist. It is my purpose tonight to review the roentgenographic changes in the skeleton in this disease and compare our current knowledge with the findings in the original reports of Cooley, Witwer and Lee.[4]

In the report of 1927, 7 patients were described and the facies (Fig. 1) of 3 of them were illustrated. These clinical aspects are of great historic interest because, according to the authors themselves, it was this feature which first led them to the recognition of Cooley's anemia. This is another example of the great value of keen

* Presented before the Wayne County Medical Society, the College of Medicine of the Wayne State University and the Detroit Roentgen Ray and Radium Society on March 14, 1957. From the departments of Pediatrics and of Radiology, College of Physicians and Surgeons, Columbia University and the Babies Hospital, New York, New York.

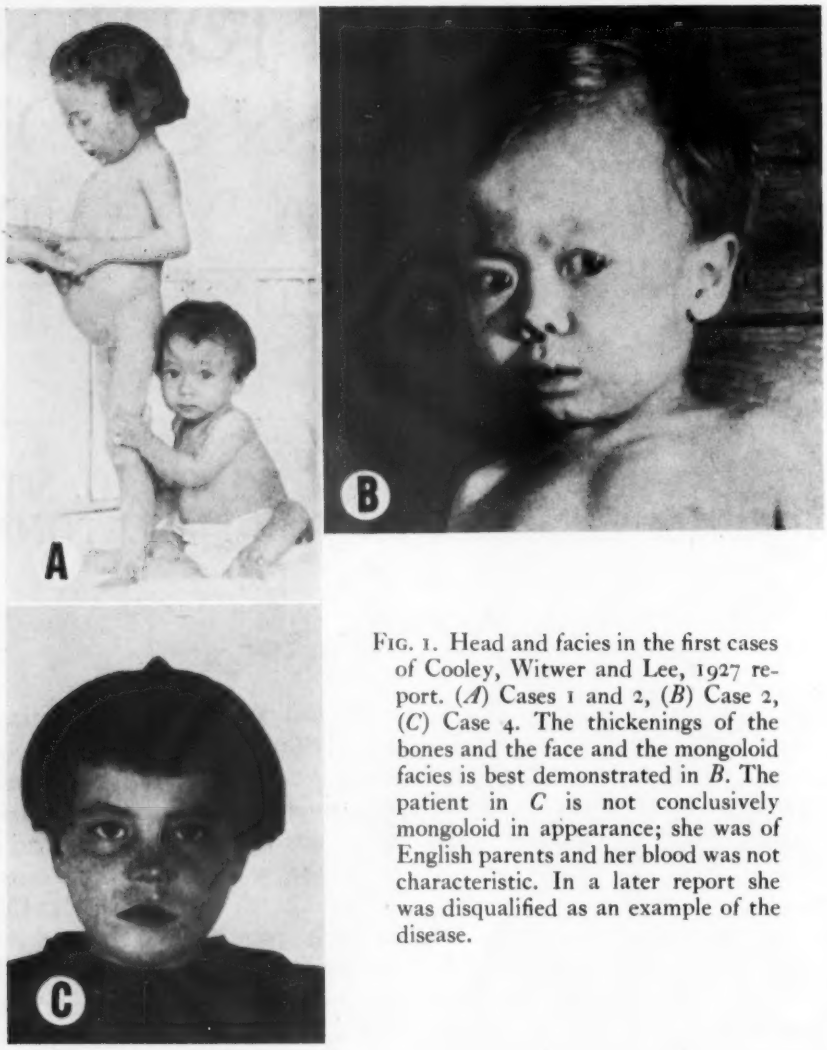


Fig. 1. Head and facies in the first cases of Cooley, Witwer and Lee, 1927 report. (*A*) Cases 1 and 2, (*B*) Case 2, (*C*) Case 4. The thickenings of the bones and the face and the mongoloid facies is best demonstrated in *B*. The patient in *C* is not conclusively mongoloid in appearance; she was of English parents and her blood was not characteristic. In a later report she was disqualified as an example of the disease.

clinical observation and interpretation in the study of disease in a world largely dominated by laboratory investigations. The ages of the 7 original patients varied between eleven and sixty months. Three patients had Italian parents, one Greek, one English, one Syrian and one was described as "mulatto." It is surprising that nucleated red cells were never found in the blood of the first patient, although this finding has now become a cardinal feature of the disease. Cooley identified transitory pericarditis in his first patient. In their later report of 1932, Cooley and Lee conceded, in retrospect, that 2 patients, the English girl and the mulatto (Cases 4 and 7), did not qualify as valid examples of their disease. The dominant Greek and Italian racial origin was not mentioned by Cooley and his colleagues in their first reports; this was first pointed out by Baty, Blackfan and Diamond.[1] Cooley and Lee stated in their third report: "We are not inclined to lay great stress on the limitation of this, or any similar disease to a particular race."

The first detailed description of the bone changes appeared in the 1927 report under the name of the radiologist Lawrence Reynolds. In these original observations, Reynolds identified and clearly described the basic changes; enlargement of the medullary cavities and atrophy of the overlying

cortical walls in the long bones, and in the tables of the calvarium in the skull. His clear and concise description is well worthy of repetition here: "The cranial bones have all shown thickening . . . , which was limited to the medullary portion, while the tables seemed unusually thin. In the earlier stages and in the less severe cases, the marrow had a mottled spongy appearance, while in the late stages there was a striking vertical striation. The long bones seemed somewhat wider than normal (Fig. 2). The cortex was unusually thin and the bone was unusually transparent as if lacking in lime. The medulla showed an unusual amount of reticulation. The ilia and scapulae also showed a marked fan-like striation. Such changes might perhaps be found in any disease in which overstimulation of the bone marrow occurred early in life, accompanied by insufficient lime deposit." In the last sentence, Reynolds explains the pathogenesis of the roentgenographic changes on the basis of overgrowth of bone marrow inside young, relatively elastic and expansile bones; and this explanation has stood the test of time. In these few words, Reynolds described accurately the basic structural changes and offered a mechanism for their genesis. His report is a composite one; individual bones in different patients are not described.

The most important new general knowledge since the first reports would probably include: (1) great extension of the racial incidence; (2) identification of mild adult cases and healthy adult carriers of the "trait" in great numbers; (3) the presence of several different types of abnormal hemoglobins in the red blood cells; and (4) demonstration of Cooley's-like changes in the skulls of several ancient peoples from several widely scattered regions of the world.

More comprehensive studies have sustained the original contention of Baty and his colleagues that the bulk of the patients are of either Greek or Italian stock, either native or emigrant. It is now clear that the disease is widely and thinly scattered on

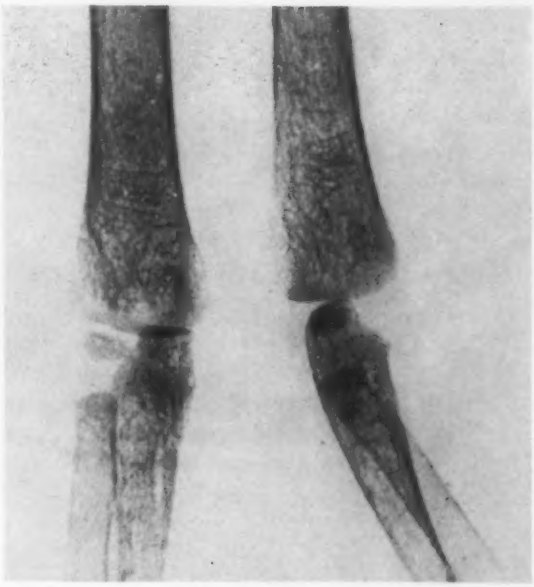


Fig. 2. Changes in the long bones from Cooley, Witwer and Lee, 1927 report. In these bones at the elbows, the rarefaction, swelling, and dilatation of the medullary cavities are all beautifully shown. In the original report the caption erroneously reads "Appearance of the bones of the legs."

the edges of the Mediterranean basin. The Mediterranean distribution suggests that the disease first appeared in Greeks who then spread it to Italy and the Mediterranean islands from which it was carried by them to other shores of the Mediterranean Sea, including Northern Africa and Asia Minor. Currently the highest concentrations of the disease are found in Greece and the Greek islands, and in the parts of Italy and the Italian islands to which they have migrated in the greatest numbers. In Italy the highest prevalence is in the lower Po valley which is northeastern Italy, and in southern Italy. The Italian islands of Sicily, Corsica and Sardinia; and the Greek islands of Cyprus and Crete are all very heavily affected; the higher incidence in these islands is explained by the tighter inbreeding in isolated populations. Cooley's anemia is exceedingly rare or nonexistent on the French and Spanish Mediterranean shores; it is claimed that there is not a single valid example of Cooley's anemia in French families of pure French descent.

The presence of Cooley's anemia in populations widely scattered on the southern shore of Asia cannot reasonably be explained on the basis of Greek origin. The disease has now been demonstrated in the natives of Persia, India, Thailand, China and the Philippine archipelago. In some parts of Thailand the incidence is believed to approximate or even exceed that of Italy and Greece.[7] The Greeks were not a maritime people at the time of European exploration of southern Asia and they have had little or no contact with the peoples residing there. Most of these explorations and colonizations were made by the Portuguese, in whom there is no Cooley's anemia currently. Story has it that Greek merchants and traders commonly travelled on the Portuguese ships and it is possible that they planted sufficient of their Cooley's-laden chromosomes to generate the Cooley's anemia which is being found with increasing frequency in southern Asia. Cooley's anemia cannot be excluded on the basis of race because it has now been reported in Greeks, Italians, Syrians, Jugoslavs, Algerians, Moroccans, Egyptians, Armenians, British, Germans, Negroes, Indians, Persians, Burmese, Thailanders, Singhalese, Chinese, Filipinos, Bukharan Jews, Mexicans, and a single doubtful case in an American Indian infant.

The recognition of the adult mild form of the disease and the hematologic stigmas in large numbers of adult healthy American Greeks and Italians is one of the most significant accomplishments since the original report of Cooley. These adults make up the potential source for the continued propagation of the severer types. Neel and Valentine[8] estimated that 1 of every 25 adult Italians in the city of Rochester, New York, either carried the trait or suffered from the mild form. Smith[9] encountered the disease

FIG. 3. Disappearance of the changes in the hand bones with advancing age. (*A*) Severe changes in the left hand of a Greek girl three years of age. (*B*) Normal bones in the same left hand at twelve years, although severe anemia and severe clinical disease persisted unabated.

in New York City in every gradation from the carrier state and the mildest form of the disease in adults, to the severe fatal type in infants. In some segments of Italy, Silverstroni and Bianco[7] estimated that 10 per cent of the population carried the trait. The principal findings which indicate the trait are: increased resistance of red blood cells to salt solutions; mild hypochromic macrocytic anemia; basophilic stippling; and the presence of excessive numbers of oval and target cells.

The presence of abnormal hemoglobins in the chronic hemolytic anemias promises to be a most important feature; it may eventually provide a new and useful method of classifying them. In Cooley's anemia, the abnormal hemoglobin F (fetal hemoglobin) has been present in high concentrations varying between 10 per cent and 100 per cent of total hemoglobin. More than one abnormal hemoglobin may be present in a single patient; the combinations of Cooley's anemia with abnormal hemoglobin S (sickle cell anemia), and with abnormal hemoglobins C, D, and E have been reported.

"Symmetrical osteoporosis" of the skull, which has been found widely in ancient skulls,[6,10] resembles Cooley's anemia both anatomically and roentgenographically. This resemblance suggests that Cooley's anemia or some other chromic hemolytic disease has existed since prehistoric times. It is conceivable that chronic severe malaria may have produced "symmetrical osteoporosis" in some cases. The disappearance of the great American Indian people, the Mayas, has been explained on the basis of the progressive lethal effect of prolonged inbreeding of a fatal racial hemolytic anemia. During 1935,[2] we studied the bloods and examined the heads roentgenographically of 1,000 living Indian children in New Mexico in a search for signs of hemolytic disease and symmetrical osteoporosis. Most of these children belonged to the Navaho, Apache, Piute and Pima tribes. Their bloods and skulls all were normal. The caves of Sicily have yielded

Fig 4. Increase in the cranial changes with advancing age. (*A*) Moderate deepening of the diploic space of the calvarium of an Italian girl eight years of age. (*B*) In the same skull at twenty-seven years, the calvarium is thicker than in *A*, and the thickened bone is more porous. This patient always had a mild anemia and mild clinical picture.

prehistoric skulls with symmetrical osteoporosis[7] which suggests that Cooley's anemia may have affected the original inhabitants of this island prior to the coming of the Greeks.

Several new roentgenographic features have been observed since Cooley's first reports. In all severe cases, both growth and maturation of the skeleton are retarded. Cooley's anemia is in fact the best example of skeletal dwarfism and infantilism caused by chronic anemia; both of these features become more pronounced with increase in age. The character and the degree of the bone changes are often modified markedly

as age increases.[3] In the more peripheral parts of the skeleton where normally red marrow is replaced early with fatty marrow, the earlier changes may disappear completely by the time puberty is reached (Fig. 3). In the skull, spine and pelvis, in which the red marrow persists throughout life, the roentgenographic changes may, in contrast, become more pronounced, even after puberty (Fig. 4). Owing to these modifications with advancing age, the hands, which are the optimal sites for the roentgen identification of the disease during infancy and early childhood, become the least diagnostic sites after puberty.

In the paranasal bones, overgrowth of marrow impedes their pneumatization from the outset and in some cases completely

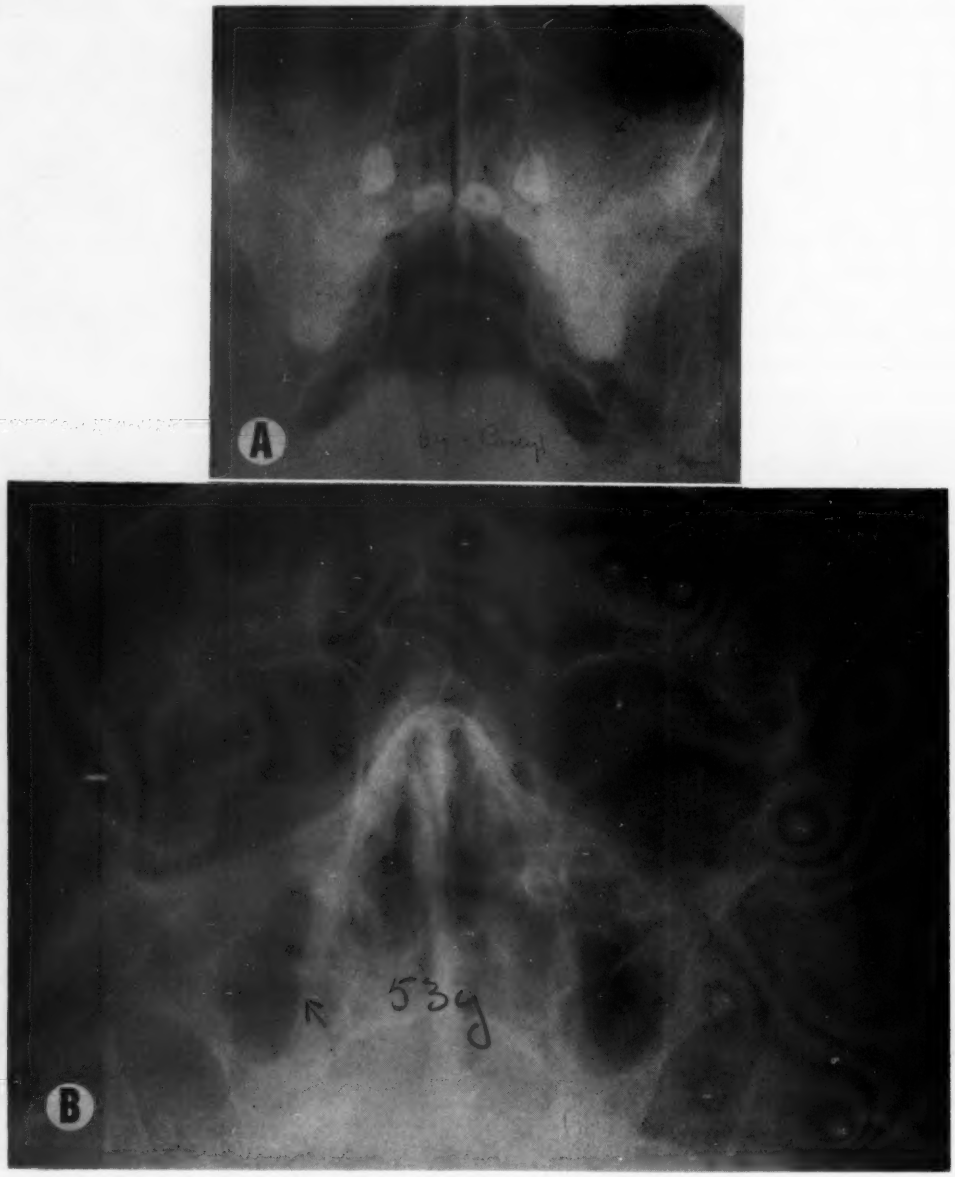


FIG. 5. Retarded pneumatization of the maxillary sinuses. (*A*) Complete in a Greek boy six years of age who had severe clinical disease. (*B*) Incomplete in a Greek man fifty-three years of age who had always had mild disease.

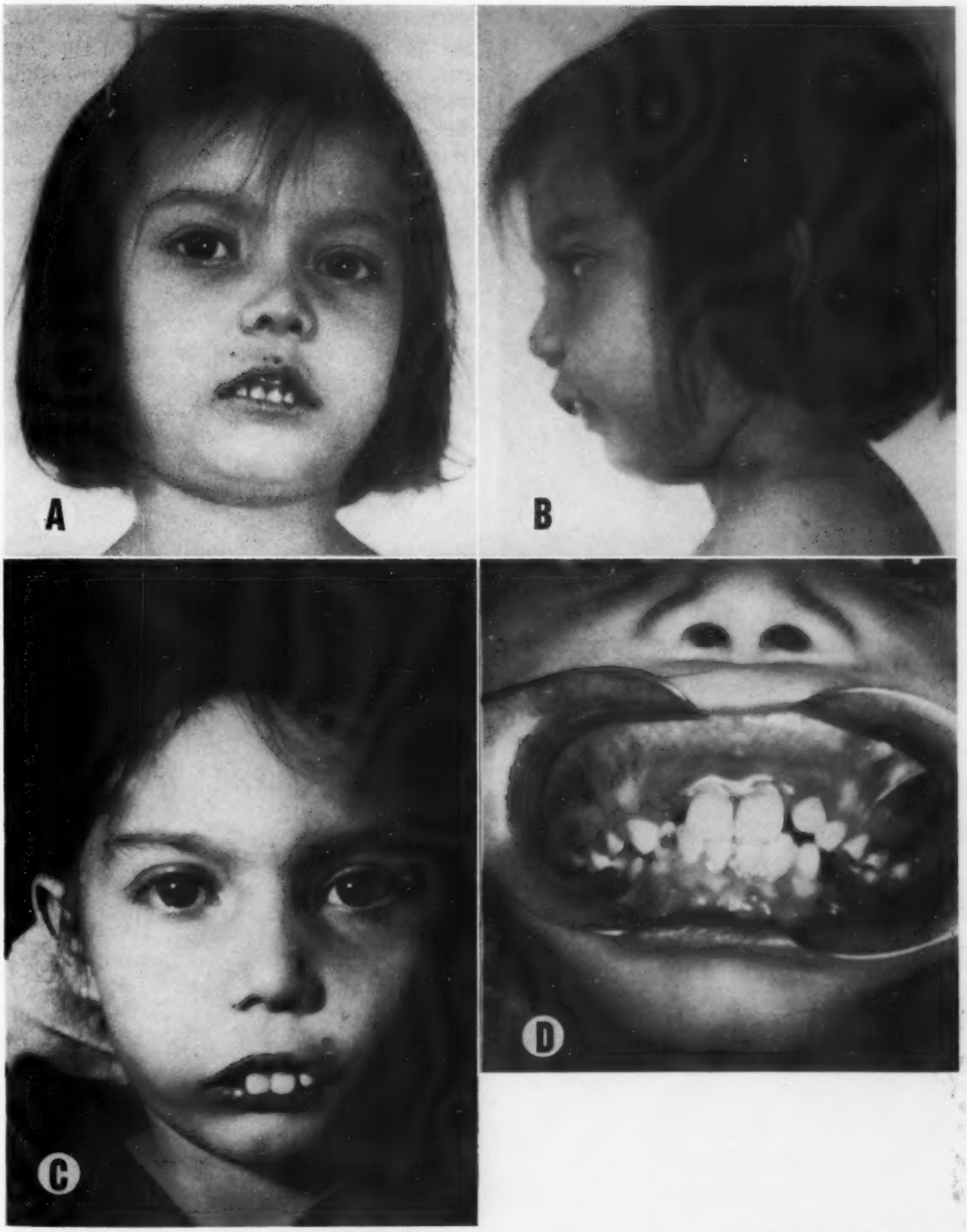
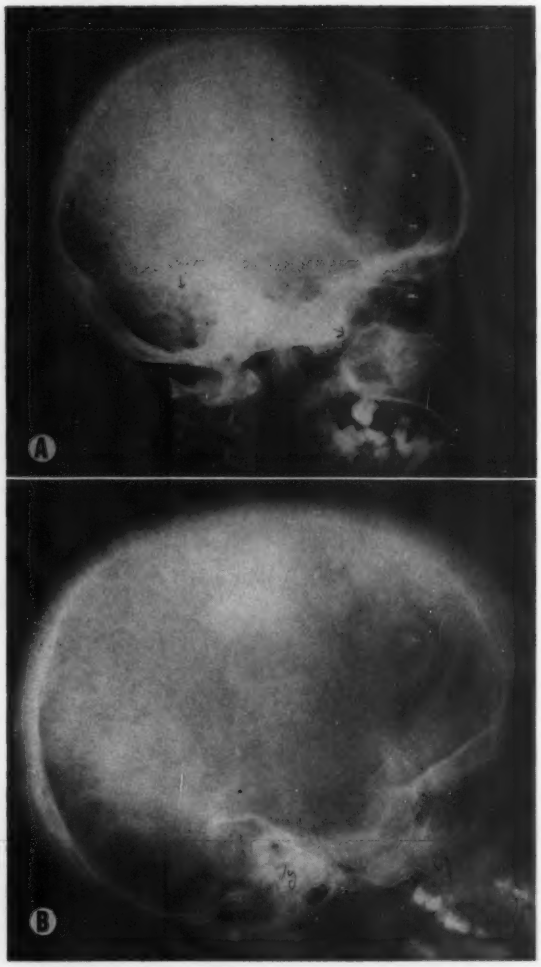


Fig. 6. Disproportionate hypertrophy of the upper maxilla with overbite on the mandible. (*A* and *B*) Frontal and profile photographs of a Greek girl three years of age which show the marked enlargement of the malar and maxillary segments of the face with protrusion of the upper incisors and retraction of the upper lip. (*C*) The same girl at six years with more pronounced enlargement of the face between the eyes and the mouth and more marked retraction of the upper lip. The exposed protruding upper incisors give a cast to the face which is more "rodent" than "mongoloid." (*D*) Artificial retraction of the lips which shows that the overbite of the upper maxilla is generalized on the mandible.



suppresses it (Fig. 5). This phenomenon is visible in the skulls illustrated in the first reports on the disease. Pneumatization is most consistently and most markedly retarded in the maxillary sinuses; in contrast, pneumatization of the ethmoidal labyrinths is not affected, probably because normally there is little or no marrow or marrow space in these bones. In the temporal bones, pneumatization may be normal or completely suppressed. The frontal sinuses may be normal, small or absent. Hypertrophy of the upper maxilla due to overgrowth of its marrow may lead to overbite on the mandible and ectopia of the teeth, especially the frontal central incisors (Fig. 6).

When the remainder of the calvarium is thickened, there is usually a conspicuous lack of such thickening in the occipital

FIG. 7 Failure of thickening of the inferior segment of occipital squamosa when there is universal thickening of the remainder of the calvarium. (*A*) Caudad to the internal occipital protuberance, the occipital squamosa is normal, notwithstanding pronounced thickening of the rest of the calvarium of a Greek girl twelve years of age. (*B*) In this thickened and striated skull of an Italian girl seven years of age, the occipital squamosa below the internal occipital protuberance is normal.

FIG. 8. Coarse patchy rarefaction of the tubular bones which suggests localized tumors of red marrow in the diffusely hyperplastic red marrow. (*A*) Hands and wrists of an Italian girl fifteen years of age. (*B*) Bones at the knees of the same patient.

squamosa below the internal occipital protuberance (Fig. 7). This is a fortunate circumstance because marked thickening on the edges of the foramen magnum would lead inevitably to compression of the underlying channels for cerebrospinal fluid and of the central nervous system itself. This segment of the occipital squamosa is probably normally deficient in marrow. In the first reports, the resemblance of the cranial Cooley's changes and those of sickle cell anemia had already been noted; since then, similar changes have been found in familial hemolytic icterus, iron deficiency anemia and in cyanotic heart disease. I have seen several cases of microcephaly due to cerebral hypoplasia, in which the diploic space became thickened and porous and resembled Cooley's anemia.

In some severe cases, localized destruction of overlying bone suggests the development of localized tumors of red marrow in the generally hyperplastic marrow (Fig. 8). In this same patient, an Italian girl fifteen years of age, vertebral bodies at several different levels were compressed in a way which suggested multiple compression deformities due to pathologic fractures (Fig. 9). In sickle cell anemia spinal changes have been found in many cases; spinal involvement in Cooley's anemia, other than enlargement of the medullary cavities of the spinal bones, is exceedingly rare.

In view of the consistent and often

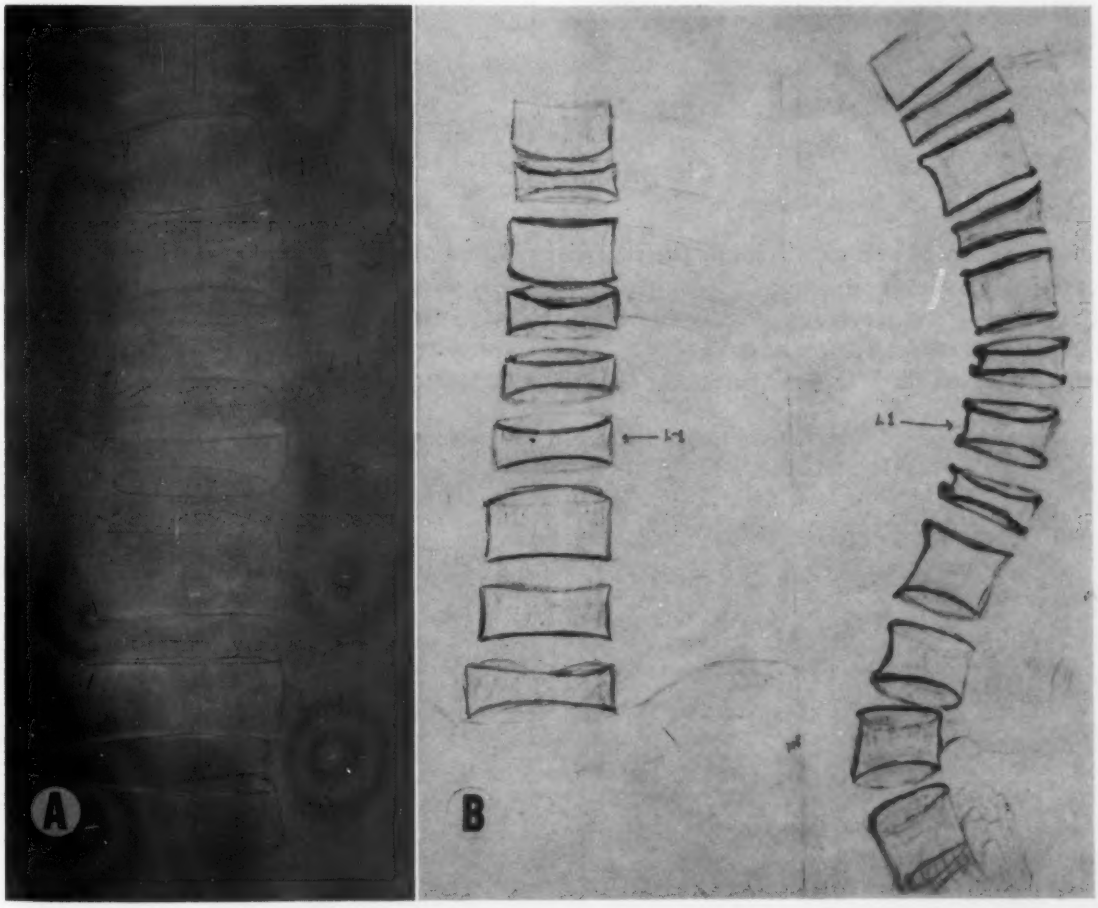


Fig. 9. Multiple pathologic compression fractures of the spine of an Italian girl fifteen years of age. (*A*) Roentgenogram of the lumbar spine in frontal projection. (*B*) Tracings of films of the same spine in frontal and lateral projections.

FIG. 10. Healing pathologic fracture of the femur of an Italian boy thirty-eight months of age with severe generalized changes in the skeleton.

marked cortical atrophy in all of the severe cases of Cooley's anemia, it is surprising that pathologic fractures have not developed more frequently. They do occur, but rarely; in children the femurs are most often affected (Fig. 10). In older persons we have seen fractures in the fibulas, metatarsals, radiuses and spine. It is my belief that the muscular weakness and inactivity which characterizes severe Cooley's anemia, protects to some degree against pathologic fractures. Baty and colleagues[1] observed fractures in 2 of their patients (Cases 17 and 18) as early as 1932.

In one of our patients, a large bony mass was found in the apex of the right hemithorax at the age of three years and it persisted and continued to grow until the twentieth year, when this Greek girl died. Roentgenographically the image suggested a large osteoma which extended off the inner edges of the first three ribs to obscure the apex laterally (Fig. 11). At the same levels on the left side, the first three ribs were deformed due to errors in segmentation with fusions suggesting a "lobster claw" deformity. There were no external clinical signs of this tumor and respiration was not disturbed. At necropsy, the mass proved to be a large shell of bone which contained red marrow and blood stained fluid in its cavity; the periosteum of the mass was continuous with the periosteum of the contiguous ribs. The presence of a similar roentgenographic change in one of Dame

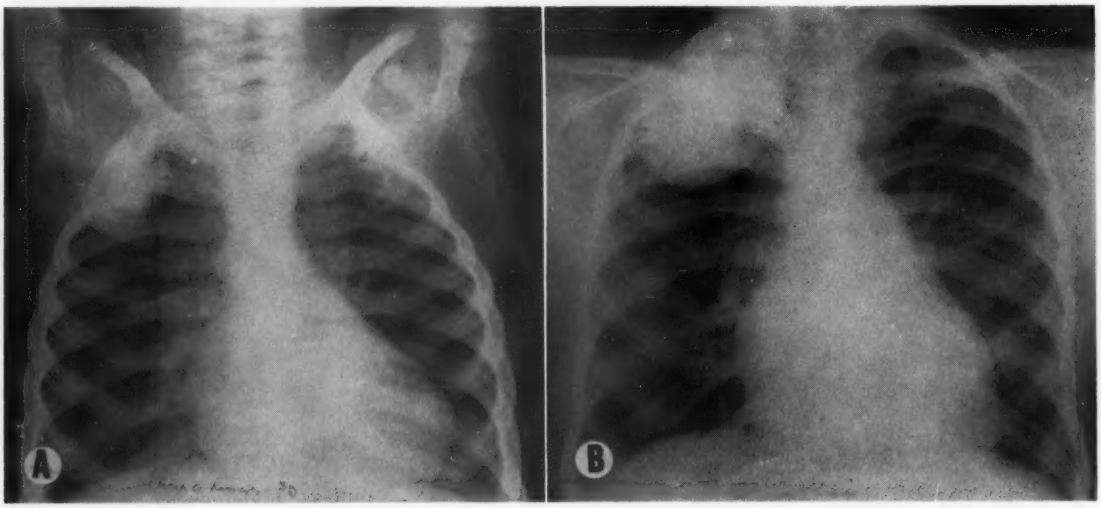


FIG. 11. Large costal osteoma of the first three ribs on the right at (*A*) three years of age, and (*B*) nineteen years of age. The first three ribs on the left side are anomalous and partially fused. The osteoma grew as age advanced.

Fig. 12. Multiple opaque gallstones in an Italian girl thirteen years of age.

shek's patients who suffered from Cooley's anemia[5] suggests that costal osteoma of this kind may be an actual complication of Cooley's anemia rather than a chance occurrence.

Gallstones are nonskeletal complications of Cooley's anemia and they have the usual roentgenographic features (Fig. 12). Their incidence increases with age and probably with the frequency of blood transfusions.

Babies Hospital
167th Street and Broadway
New York, New York

REFERENCES

1. Baty, J. M., Blackfan, K. D., and Diamond, L. K. Erythroblastic anemia; clinical and pathologic study. *Am. J. Dis. Child.*, 1932, *43*, 667–704.
2. Caffey, J. Skeletal changes in chronic hemolytic anemias (erythroblastic anemia, sickle cell anemia, and chronic hemolytic icterus). Am. J. Roentgenol. & Rad. Therapy, 1937, *37*, 293–324.
3. Caffey, J. Cooley's erythroblastic anemia; some skeletal findings in adolescents and young adults. Am. J. Roentgenol. & Rad. Therapy, 1951, *65*, 547–560.
4. Cooley, T. B., and Lee, P. Series of cases of splenomegaly in children with anemia and peculiar bone changes. *Trans. Am. Pediat. Soc.*, 1925, *37*, 29.
   Cooley, T. B., Witwer, E. R., and Lee, P. Anemia in children with splenomegaly and peculiar changes in bones; report of cases. *Am. J. Dis. Child.*, 1927, *34*, 347–363.
   Cooley, T. B., and Lee, P. Erythroblastic anemia; additional comments. *Am. J. Dis. Child.*, 1932, *43*, 705–708.
5. Dameshek, W. "Target cell" anemia. Anerythroblastic type of Cooley's erythroblastic anemia. *Am. J. M. Sc.*, 1940, *200*, 445–454.
6. Hooton, E. A. The Indians of Pecos Pueblo: A Study of Their Skeletal Remains. Chapter X, Pathology. Yale University Press, New Haven, Conn., 1930.
7. Les Thalassémies in: Reports of the 15th Congress of French-speaking Pediatricians; May 23, 24 and 25, 1956; 2 volumes. Société Provencale d'Imprimerie et de Cartonage, Marseilles, Boul. Michelet 36.
8. Neel, J. V., and Valentine, W. N. Frequency of thalassemia. *Am. J. M. Sc.*, 1945, *209*, 568–572.
9. Smith, C. H. Detection of mild types of Mediterranean (Cooley's) anemia. *Am. J. Dis. Child.*, 1948, *75*, 505–527.
10. Williams, H. V. Human paleopathology; with some observations on symmetrical osteoporosis of skull. *Arch. Path.*, 1929, *7*, 839–902.

HYPOPHOSPHATASIA*

GUIDO CURRARINO, M.D., EDWARD B. D. NEUHAUSER, M.D.,
GERTRUD C. REYERSBACH, M.D., AND EDNA H. SOBEL, M.D.
BOSTON, MASSACHUSETTS

HYPOPHOSPHATASIA is the term applied to a chronic familial disease of uncertain etiology, affecting primarily children, in whom defective bone formation is associated with low alkaline phosphatase activity in the serum and tissues.

This association was first recognized by Rathbun in 1948[1] but probable cases were described earlier[2–7] and several others have been reported since.[8–14]

While the disease resembles rickets histologically, the roentgenologic abnormalities and many of its clinical manifestations distinguish it from all other disorders of bone.

The purpose of this paper is to outline the major features and to draw a more complete picture of the disease.

The material used in this study is summarized in Table 1 and detailed in the Section "Report of Cases." It includes data on patients previously reported and on several new ones gathered from various sources. Additional clinical information and roentgenologic and histologic documentation on patients mentioned in the literature was obtained through the courtesy of the authors or private physicians. Some probable instances in which information on serum alkaline phosphatase activity was not available are included.*

CLINICAL FEATURES

Tabulation of the patients according to their age at the onset of the symptoms reveals, in general, a decrease in degree of severity of the disease as the age increases. It shows, in addition, that the patients of the same age group are usually affected by the disease in a similar fashion. The time of the onset cannot always be determined with accuracy, but there is evidence, at least roentgenographically, that it can start in utero, as in the newborns, or in postnatal life, as is probable in most other instances. The newborns, the infants and the children will be considered separately, although there is some overlap in the disease picture presented by patients of different ages.

Newborns. In the first 6 patients (Table 1), the clinical features were identical. Each was born at term with a globular and "boneless" skull, soft skeleton, and severe deformities of the extremities. They failed to breathe or breathed poorly. The first 5 patients died within the first hour of life. The sixth lived nineteen days with considerable respiratory difficulty and cyanosis.

Patients 7, 8, and 9 died between the ages of two and six months. Clinically, their skeletal deformities were somewhat less severe than in the previous cases. These abnormalities were generalized and undoubtedly present at birth, but were noted only a week or so thereafter when the symptoms became apparent. The common symptoms and signs were irritability, jerky movements or convulsions, failure to gain weight, and slow growth in length and in head circumference. Cyanosis, anorexia, vomiting, constipation, loud cries and fever were prominent, but not constant, features.

Infants. In the next 14 cases (Patient 10-23), the symptoms appeared gradually between the first and the sixth month of life after a period of apparent good health. The clinical picture was characterized by anorexia, vomiting, constipation, failure to thrive or grow, recurring episodes of unexplained fever, irritability, and hypotonia. Convulsions, cyanosis, and episodes of "loud cries" were noted in some patients. The cranial sutures were separated, the anterior fontanelle was wide, bulging, and

* Mention is also made in the literature (Reference 12b) of a case each by L. Emmett Holt, Jr. and R. Ulstrom. These patients are not included as the data available are too incomplete.

* From The Children's Medical Center and Harvard Medical School, Boston, Massachusetts.

TABLE I

No.	Reference No.	Year Born and Sex	Age at Onset of Symptoms	Outcome	Alkaline Phosphatase	Serum Calcium Mg. Per Cent	Urine Albumin	Renal Function Impairment	Wide Sutures	Craniostenosis	Loss of Teeth	Affected Siblings	Father's Phosphatase	Mother's Phosphatase
1	*	1951 F	birth	d. birth					yes			1:1		4 BU
2	*	1951 F	birth	d. birth					yes			1:3		
3	*	1929 M	birth	d. birth					yes					
4	*	1952 M	birth	d. birth					yes			2:3		
5	*	1954 F	birth	d. birth					yes					
6	*	1945 F	birth	d. 19 da					yes			2:3	0.88 BLU	0.66 BLU
7	1	1946 M	10 da.	d. 2 mo.	0.0–0.7 BLU	13.6–10.9	mild	mild	yes			1:1		1.4 BLU
8	4 (Case 1)	1932 F	10 da.	d. 3 mo.		15.5–15.8	mild		yes			2.3†		
9	4 (Case 2)	1934 F	10 da.	d. 6 mo.		14.3–18.4	yes	no	yes					
10	5 (Case 1)	1935 M	6 wk.–6 mo.	d. 8 mo.					yes			2:2†		
11	5 (Case 2)	1937 F	birth–3 mo.	d. 10 mo.		11.6	yes		yes	(?)				
12	9a (Case 3)	1944 M	3 mo.	d. 8 mo.	0.3–1.6 BU	10.8–14.8	yes	yes	yes			2:3	0.95–1.11 BLU	0.59–0.42 BLU
13	9a (Case 4)	1947 F	1 mo.	d. 8 mo.	0.9–2.8 BU	12 –14.7	mild	yes	yes					
14	10	1952 F	3 mo.	d. 10 mo.	3.3–4 BBU	9.5–14	yes	yes	yes			1:2		
15	*	1954 F	4 mo.	d. 9 mo.	1.2 BU 2.4 KA	13.5	no		yes			1:2	1.2 BU 4.6 KA	1.7 BU 3.9 KA
16	*	1953 F	1 mo.	a. 2 yr.	0.75–1 BU	9.5–12	mild	no	yes	yes		1:3	4.4 BU	1.5 BU
17	13a (Case 1)	1952 F	1 mo	a. 2 yr.	2–9 KA	10 –14.8	yes	yes	yes	yes		1:2	5.7 KA	5.6 KA
18	*	1952 F	2 mo.	a. 2 yr.	"low"	"normal"	no	no		yes	yes		"normal"	"low"
19	11	1953 M	2 mo.		"low"	"high"			(?)			2:2†		
20	12a	1954 F	3 mo.	a. 16 mo.	0.89–1.38 BLU	10.7–16.0	mild	mild	yes	yes			0.77–1.13 BLU	0.57–1.11 BLU
21	13a (Case 2)	1952 F	3 mo.	a. 3 yr.	3–7.3 KA	10.7–10.8	no	no	yes	yes		1:1		
22	6 (Case 2)	1934 F	3 mo.	a. 4 yr.	1.5–2.12 BU	16.2–11.7	no	mild	yes	yes	no			
23	9a (Case 5)	1950 F	4 mo.	d. 29 mo.	0.4–1 BU	High only terminally	no	only terminally	yes	yes		1:1	1.4 BU 0.51 BLU	1 BU 0.77 BLU
24	13a (Case 3)	1951 F	2 yr.	a. 2–10/12 yr.	2.4–6.3 KA	12.1	no	yes		yes		1:2		
25	8 (Case 1)	1936 M	1–2 yr.	a. 19 yr.	0.22–0.7 BU	19 –11	no	no		(?)no	no	2:3	1.8 BU	2.8 BU
26	8 (Case 2)	1938 M	1–2 yr.	a. 17 yr.	0.39–4.3 BU	19 –10.4	no	no		(?)no	yes			
†27	9a (Case 1)	1948 F	17 mo.	a. 6½ yr.	0.84–1.64 BLU	9.8–10.3	no	no		no	yes	1:1	1.01 BLU	2.38 BLU
28	9a (Case 2)	1949 M	17 mo.	a. 3½ yr.	0.2–0.7 BU	9.5–10.2	no	no		no	yes	1:2		0.66 BLU
29	9a (Case 6)	1943 F	8–10 mo.	a. 8 yr.	1.6–7.6 BU, 0.83 BLU	10.1–10.9	no	no		no	yes	3:4		
30	9a (Case 6′)	1944 F	15 mo.	a. 7 yr.	10.8 BU (?)	8.2				no	yes			
31	9a (Case 6*)	1949 M	18 mo.	a. 2-3/12 yr.	5.3 BU	8.4				no	yes			
32	2	1922 M	4–5 yr.	a. 4-10/12 yr.		9.9				no	no	1:7†		
33	14	M	5 mo.	a. 4 yr.	4–5.5 JKU	10.8–11.5	no				yes	1:1		

* Not previously reported.
† Reference 12, Page 443.
Patients in braces are siblings.
BU—Bodansky units (normal: infants 10–20, children 5–10, adults 2–3.5).
BLU—Bessy-Lowry units (normal: infants 6–11, children 3.8–7.5, adults 1.8–3.2).
KA—King-Armstrong units (normal: infants 15–35, children 15–20, adults 5–10).
JKU—Jenner-Kay units (normal for children 4–12).
BBU—Buch and Buch units (normal for infants 10–20).

often tense, and the scalp veins were prominent. In most cases, there was a rachitic rosary and the ends of the long bones were enlarged.

These features progressed rather rapidly for a few months; then improvement was observed in all those patients who survived and were followed. However, 5 patients (Patient 10, 12, 13, 14 and 15) died between the eighth and tenth month of life, at the peak of the disease. One (Patient 23) died at twenty-nine months, probably from other causes. In the surviving patients who were followed, despite the gradual subsidence of the symptoms, the skeletal deformities persisted and often became worse. They started to walk late, developed genu valgum, and some of them were short in stature. Two lost their deciduous incisors prematurely. Craniosynostosis occurred in all during the second year of life but this led to symptoms in only a few. Gradually, these patients became indistinguishable from those of the next group in most clinical features and in the course of the disease.

Children. Patients 24 to 33 came under observation between the seventeenth month and the thirteenth year of life, although mild manifestations of the disease could be traced back to early childhood or infancy in a number of instances. The usual complaints included delayed onset of walking, defective gait, knock knees, painful extremities, marked dental caries (with premature loosening and then loss of deciduous teeth, usually incisors), and, occasionally, short stature. A rachitic rosary and enlarged bone ends were other prominent features. Premature craniosynostosis was demonstrated in only 1 instance (Patient 24).

None of these patients died during the period of observation and, at most, very slow improvement occurred in the children who were followed.

LABORATORY FINDINGS

No laboratory investigations were performed in the patients who died in the newborn period (Patient 1–6). In the others, the following data were recorded.

The hemogram was within normal limits, except for Patients 7, 8, and 9 and for several of the infants, who, during the florid stage of the disease, had slight to moderate anemia and leukocytosis. The differential blood cell count was normal. In 2 infants (Patient 16 and 23) the bone marrow showed myeloid hyperplasia.

The blood cultures, agglutination tests, and serology were uniformly negative, as was the serology of the parents. The total serum proteins, sedimentation rate, liver function tests and serum electrolytes were within normal limits. Spinal fluid determinations and ventriculograms showed no specific abnormalities.

The serum calcium was elevated in those newborns who were investigated, in most infants but in only 3 of the older patients. In several of those who had hypercalcemia, some normal serum calcium values were observed.

The serum phosphorus did not vary significantly or uniformly from the normal.

The serum alkaline phosphatase was decreased. Apart from fluctuations, which might have been fortuitous, the levels remained low. When histochemical or biochemical examinations were performed the alkaline phosphatase was also found to be abnormally low in bones, kidneys and other tissues (Patient 7, 14, 16, 17 and 27).

Urinary abnormalities were usual in the newborns and infants with hypercalcemia and consisted of varying amounts of albumin, white blood cells, and casts. Mild to moderate impairment of renal function was also common in these patients but was exceptional in the childhood group. Urine cultures were uniformly negative and urologic investigations never showed any structural abnormality.

The urinary calcium excretion, by actual measurements or in terms of the Sulkowitch test, varied from slightly decreased to slightly increased. These variations were usually unrelated to the serum calcium levels. Calcium balances were always positive but not markedly so (Patient 7, 8, 9 and 17).

Ethanolamine phosphoric acid, an amino acid which is not present in normal urine,

was found in the urine of all patients in whom appropriate investigations were made (Patient 17, 19, 20 and 27).

ROENTGENOLOGIC CHANGES

Roentgenologically, the basic skeletal abnormalities common to all patients, whether severely or mildly affected, consisted of diminished and irregular bone formation in the presence of continuing proliferation of the pre-osseous tissue.

In the Newborns (Patient 1–6, Fig. 1–5), these changes were of marked degree and involved the entire skeleton. Many parts were wholly uncalcified while others showed ossification only at their central portions. These bones were short and thin and had a coarse trabecular architecture with ragged ends and contours. In some long bones, the major changes were observed in the metaphyseal region where the ossification was streaky, spotty, and irregular and where there was a considerable amount of poorly calcified material left behind in the growth process. Metaphyseal infractions were common. The deformities and diminution in length of the extremities noted clinically were in great part secondary to angulations and fractures. Abundant callus was present at many fracture sites.

The findings in Patients 7, 8, and 9 were less severe. Perhaps in these instances the disease was milder or started later in fetal life.

In most cases included in the *Infant* group (Patient 10–23), the first roentgenograms were obtained when the disease was already advanced and the patients were beyond the newborn period. In some, the roentgen changes resembled those of the less severely affected newborns, and it is possible that here the disease started before birth and remained asymptomatic for some time. In others, the changes must have had their onset in the postnatal life. Examples of the latter type are Patients 16 and 23. Patient 23 (Fig. 9) had roentgenograms taken in the newborn period for clubfeet and congenital angulations of long bones associated with overlying skin dimples. Apart from these anomalies, the bones were reported normal in development and architecture. Roentgenograms taken three or four months later showed the full-blown picture of the disease. Patient 16 (Fig. 8) had roentgenograms taken at the very onset of the symptoms, at about the age of one month, and was then followed regularly. The following is a description of the type and course of the bone changes in this patient. The first roentgenograms showed only congenital angulation of tibiae and fibulae and skin dimples, faint nonspecific bands of decreased density in most metaphyses and slight prominence of the cranial sutures. The metaphyseal rarefaction gradually increased and the zone of provisional calcification became indistinct. Demineralization continued along the margins of the cranial bones and especially in the small ossification centers of the extremities. By the sixth month, diminution and irregularity of bone deposition had also become evident as the disease advanced. There was marked and progressive widening of the sutures and the soft tissues of the anterior fontanelle bulged. In the long bones, the epiphyseal lines were wide and irregular and the metaphyses appeared spotted, streaky and markedly demineralized. The metaphyseal infractions were accompanied by abundant subperiosteal new bone formation. The margins of many diaphyses had also become irregular and fuzzy. Several small centers of ossification had developed a mottled sclerosis while others were late in their appearance. Between the eighth and twelfth month, both roentgenographic and clinical improvement began. In the skull, the healing process was accompanied by premature closure of the sutures. In the roentgenograms taken at the twentieth month, the cranium had the typical shape and pattern of total craniosynostosis. In the rest of the skeleton, healing was rapid at first but then progressed slowly. The improvement consisted of remineralization of the metaphyses and of the small ossification centers accompanied by a gradual remodeling of the shafts. In a few long bones, healing was complete; in others it remained partial, leaving an uneven widening of the

entire epiphyseal line with residual irregular areas of various size projecting into the metaphyses. In these bone ends, some short segments of the epiphyseal line and the adjacent zone of provisional calcification appeared normal. Some flat bones became normal while others continued to show marginal scallopings. However, some coarsening of the trabecular architecture and undertubulation remained in most previously involved areas. Once this stage of the disease was reached, the roentgenologic changes became indistinguishable from those of most patients in the next group.

All of the other infants of the same group showed changes comparable to those seen at some stage in Case 13. In those instances in which serial roentgenograms were available, the sequence of events was similar. In some patients, the early stage of metaphyseal demineralization lasted for a longer period, while in the others the end stage was reached more rapidly. Wide sutures were observed in all patients and premature craniosynostosis took place in all those infants who were observed through the second year. The skulls of some of these patients, together with the well-known shape and pattern of total craniosynostosis, presented an unusual rounded bony prominence in the region of the anterior fontanelle where soft tissue bulging had been present. Congenital angulation of long bones, with overlying skin dimples, was reported in a number of these patients, as well as in some newborns.

In all patients included in the *Childhood* group (Patient 24–33), the bony abnormalities were already well developed in the first roentgenographic studies. They were either generalized, involving all the growing parts of the skeleton, or were limited to a few bones. Occasionally, they were minimal in degree. The sites most commonly affected were the distal ends of the femora and upper ends of the fibulae and humeri. Flaring of the ribs and scalloping of the iliac crests and scapulae were common. The epiphyseal lines were widened and uneven and often showed irregular tongues or rounded areas of uncalcified or completely radiolucent tissue projecting into the metaphysis. Coarse metaphyseal architecture was commonly present in the involved bones and also in some areas which previously had apparently been more severely involved. These findings, and the shortening of the extremities observed in some patients, indicate that the changes must have started early in life. Craniosynostosis was demonstrated only in 1 case (Patient 24). The teeth were reported to be defectively mineralized in Patient 27.

Follow-up examinations showed that in some bones the process slowly subsided, while in others the metaphyseal features remained essentially unchanged over many years. However, bone growth continued in some cases at a normal rate, and in others at a somewhat reduced rate. The last roentgenograms on Patient 25, taken at the age of nineteen years when the epiphyses had closed, showed a residual alteration of the architecture in the previously involved segments where there still remained a few scattered, irregular areas or radiolucency.

PATHOLOGIC FINDINGS*

Four autopsies have been reported (Patient 7, 8, 9 and 14), and 3 of these were from the transitional subgroup between the newborn and infant. The other patient was in the infantile group. Biopsies of bone from 3 other patients in the infant and children groups have also been described. To this material we add 4 autopsies (2 of newborns and 2 of infants) and 1 biopsy of the costochondral junction of another infant.

The pertinent pathologic findings were limited to kidneys and bone; disturbances of other tissues were inconstant and of doubtful significance.

In all 4 published autopsies, there was renal pathology consisting principally of low-grade nephritis and scarring. There were calcific deposits in the tubules and peritubular tissue in 3 cases, and in the other the casts did not contain calcium but

* By Jonathan Cohen, M.D., Children's Medical Center, Boston, Massachusetts.

stained metachromatically. The material from our 2 infants confirmed these findings of low-grade inflammation, of minimal degree, and peritubular calcification with formation of calcified casts. The autopsies of our 2 newborns (Patient 1 and 2) showed no demonstrable renal abnormalities.

The pathologic studies of the bones revealed a disturbance similar in type in all instances but varying widely in degree. In the newborns, the skeletal defects were generalized. The cranial bones were small and soft, and often resembled plaques encased in the walls of a fibrous sac. Our material, unfortunately, does not allow adequate histologic description of the sutures, but grossly, it is evident that the sutures presented a normal pattern with the anlage of each cranial bone separated from its neighbors by well-defined fibrous demarcations. Histologically, much of the grossly fibrous tissue contained osteoid. The fibrous demarcation should be especially noted in connection with the development in some older children of craniosynostosis, in order to point out that an anomaly involving absent sutural demarcations has not been demonstrated.

The extremities were short and variably bowed, with thickening of the ends of the bones. They were soft to palpation, and showed multiple fractures, most of which contained callus. Deformities of the chest (rachitic rosary or pectus excavatum) were minimal in the newborns but significantly present in the infants. Microscopically, the long bones showed no abnormality of nonproliferative portions of cartilage. The zone of proliferating cartilage cells, however, was somewhat wider than usual, and the hypertrophic cell zone was considerably involved. It was irregular, and its width was many times that seen in the neonatal period, even when compared with that of premature infants. The border of the cartilage adjoining the bone marrow was grossly irregular, and long tongues of cartilage cells reached far into the marrow of the diaphysis. The metaphyseal area often showed marked distortion of its trabecular pattern by previous fractures with repair, and large amounts of osteoid constituted the predominant metaphyseal tissue. In those bones in which metaphyseal fractures had not distorted the trabecular arrangement, the individual trabeculae seemed broader than usual, although oriented properly. The diaphyseal portions, when angulation or fractures had not distorted the alignment, displayed a much more primitive and cancellous structure than is usual in the compacta at this age. There also occurred, in all the bones examined, a wide zone of subperiosteal bone formation cloaking the cortex.

In the infants, the bony changes were nearly identical histologically with those of the newborns. All growing cartilage, *e.g.*, epiphyseal cartilage, costochondral junctions, etc., showed striking disturbances. The increase in width of the proliferating cartilage and the marked widening of the hypertrophic cell zone with irregularity of cell column formation, the irregularity of penetration of hypertrophic cells by the marrow, and the persistence of long tongues of cartilage in the marrow were universally present. In the metaphysis the occurrence of osteoid in large amounts and the disturbance in trabecular architecture attendant upon this, or secondary to fracture, were also common. Where stains for alkaline phosphatase were made on such material, little or no activity was found, and the histochemical findings were verified microchemically in several instances. One observation which was made on our material was the absence in callus of any significant amount of cartilage, usually a prominent constituent in this age group. The callus was well formed and abundant, but its amount was several times less than one would expect in newborns or normal infants. No consistent morphologic change in the osteoblasts or osteoclasts, or decrease in their number was noted.

Although the clinical material forming the childhood group represents nearly one third of the cases, reports of 2 biopsies of bone constitute all the available histologic

data from patients of this group. The patient described by Sobel, *et al.*[9] was twenty months old at the time of biopsy and showed findings identical with those of the infant group. The fibula of a six year old boy, described by Hühne and Schönfeld,[2] showed no significant changes in the diaphysis, but in the metaphysis there were traces of osteoid, islands of cartilage cells, and irregularity of the trabeculae. The epiphyseal cartilage itself was slightly widened and irregular, and projected tongues of cartilage cells into the metaphysis, but these changes were considerably milder in degree than in the infant's specimens. The hypertrophic cell zone was quite wide.

No pathologic material has been reported or is available to us from patients in the adult group.

In the newborns, the gross pathologic picture resembled osteogenesis imperfecta, while in the infant and childhood groups there was a greater resemblance to rickets. The histology of the long bones in all groups resembled rickets in the type of alteration, in endochondral sequences, and in the occurrence of osteoid, but the severity of the changes seen in all autopsy material, especially in the neonatal and young infants, was far beyond those resulting from vitamin D deficiency. The extreme diminution in bone formation and the prevalence of osteoid in the cranial bones were findings not encountered in rachitic infants. In the older patients, the degree of change was milder and more variable, and therefore, the findings in some biopsies were reported as indistinguishable from rickets, but differential diagnosis on histologic grounds sometimes could be made since the changes were out of proportion to the age of the patient and the clinical history.

DISCUSSION

On the basis of the more fully investigated patients included in this survey, there is little doubt that hypophosphatasia is a definite entity, quite unlike any other bone disease. The patients not completely studied, or in whom the serum phosphatase activity is not known, have been included because they presented a combination of some of the following characteristic features: type of roentgenologic appearance, histologic changes, low phosphatase in parents, occurrence of the disease in siblings, type of cranial bone involvement, premature loss of deciduous teeth, failure to respond to vitamin D therapy, hypercalcemia, and renal damage. The variation in the roentgenologic and histologic abnormalities in individual cases reflects the variation in the degree of severity with which the disease can manifest itself.

The interpretation of the pathogenesis of the disease has been focused principally on the low phosphatase of the serum, bones, and other tissues. The cause of this enzymatic abnormality is not known. No inhibiting agent has been found[9,10,12] in the serum and the search for exposure to substances such as beryllium or fluorine which might inactivate phosphatase has been unsuccessful.[9] The finding of low phosphatase in many of the parents, the familial incidence of the disease and its occurrence in newborns suggest that the deficiency of phosphatase may be congenital and genetically determined.

Since many parents, and an occasional normal sibling, also showed similar serum abnormality without evidence of bone disease, no simple relationship between these two findings can be considered likely. Histochemical examination of the bones of the hypophosphatesemic parents of affected children has never been performed. In the bones of affected children, histologic examination showed abundant cartilage, osteoblasts and matrix, but there was a marked deficit of alkaline phosphatase activity (Patient 7, 14, 16, 17 and 27). As the osteoblasts produce both osteoid and phosphatase, it is not clear whether, in addition, the matrix itself is abnormal. Fraser and co-workers[12] have recently demonstrated that the serum of one patient could support calcification of rachitic rat cartilage. However, the patient's costochondral junction did not calcify either in normal serum or in

a synthetic medium, although that of a child with vitamin D refractory rickets did calcify under the same circumstances.[18]

The hypercalcemia and the renal changes are probably interrelated, but their origin and sequence are not clear. The hypercalcemia may be secondary to the failure of calcium deposition, as Schlesinger *et al.*[13] have suggested, and is possibly enhanced by some inability of the kidneys to fully excrete calcium. Either of these mechanisms could account for the ready rises in serum calcium levels noted in some of the patients to whom large doses of vitamin D were given. Hypervitaminosis D or hypersensitivity to this vitamin cannot be established on the basis of the data available. The entire syndrome, including hypercalcemia, was also observed in small infants who never received vitamin D. The renal changes have been thought to be secondary to hypercalcemia. It is difficult, however, to ascribe them entirely to it since the studies of calcium balance and excretion do not point toward an excessive loss of calcium in the urine. The question of another defect was raised by McCance *et al.*[11] and Fraser *et al.*[12] and confirmed by the observations made on Patients 17 and 27. They demonstrated the presence of ethanolamine phosphoric acid in the urine and serum of patients with hypophosphatasia and their parents, but its specificity is doubtful since it has been found in other diseases.

The involvement of the skull as seen in this disorder is most unusual. It occurs less frequently in children in whom the disease is mild and starts late. The widening of the sutures may be in great part due to failure of calcification of the pre-osseous substance along the growing margins of the cranial bones. The bulging of the soft tissues of the fontanelle most likely reflects a discrepancy in the rate of growth of the skull and brain. The evolution of craniosynostosis is not clear. It is of interest that this anomaly has also been seen in some instances of idiopathic hypercalcemia and in an occasional patient affected by vitamin D resistant rickets.

The variation in clinical manifestations seems to be related chiefly to the age of the patient at the onset of the disease; the most severely affected are those in whom the disease starts in utero or in early infancy. When the disease occurs in more than one sibling, the patients present practically identical features. Its severity is not consistently reflected by the level of the serum alkaline phosphatase in the patients or their parents. Hypercalcemia and renal damage in infancy usually make the prognosis worse. The cause of death in those patients who die of the disease is not always clear. In the patients who died in the newborn period death was probably due to respiratory failure secondary to poor ossification of the thorax, while in older ones it was interpreted as being chiefly renal in origin. In those who survive the first year of life, improvement is to be expected but residual and even prominent skeletal deformities and, in some instances short stature, may be observed. The permanent teeth have so far been well rooted and normal in appearance.

What abnormalities these children will present as adults and whether or not their offspring will be affected is not known. In this regard, mention should be made of a report by Macey[7] in 1936. He described 2 brothers who came to medical attention in adult life for multiple fractures after minor trauma, complicated by delayed union. Both showed abnormally low alkaline phosphatase levels but otherwise normal serum chemistry. One of them had had marked rachitic skeletal deformities in childhood and as an adult was reported as showing a dolichocephalic skull with prominent eyes (craniosynostosis?). Albright and co-workers[17] have recently reported at one of the New England roentgenologic meetings a similar patient whose children showed low phosphatase but no bone disease. Roentgenographically, apart from fractures with delayed union and secondary deformities, the bones in these patients were apparently normal. These cases are considered separately as it is not yet certain whether they

display a late result of the disease in childhood, are affected by an adult form of hypophosphatasia, or represent an entirely different entity.

The disease is not limited geographically, as it has already been observed in Canada, England, Germany, and Italy,* and the United States. Two of the patients (Patient 3 and 15), surveyed in this report were Negroes. The disease does not appear to be sex linked and often occurs in siblings. Often one or both parents and an occasional sibling show low values of serum alkaline phosphatase without demonstrable bony abnormality. This material was examined from the genetic point of view by Dr. Arthur G. Steinberg,† who made the following comments:

COMMENTS ON THE GENETICS OF HYPOPHOSPHATASIA

In these data the propositus (index case) in the families with more than one affected child is not indicated. If it is assumed that there was but one propositus per family, the computed frequency of the disease among the sibs of the propositi is 28 per cent. On the other hand, if every case was discovered independently (that is, if every patient was a propositus) the derived frequency of the disease among the sibs of the propositi is 40 per cent. The former situation is more likely to be true than the latter, for when an affected child draws attention to a family, it is usual for all children in that family to be followed. Hence, the frequency of the disease among the sibs of the propositi is probably closer to 28 per cent than to 40 per cent. Twenty-eight per cent, based on a sample as small as this one, is not significantly greater than the 25 per cent which would be expected if hypophosphatasia is due to an autosomal recessive gene.

Information concerning the presence or absence of consanguinity between the parents of the affected children could have contributed to the genetic analysis, because an increased frequency of consanguinity is expected among the parents of children suffering from a rare recessive disease. Four sets of parents were reported to be unrelated, but no information was provided for the remaining twenty one pairs of parents.

The ratio of 2 females to 1 male among the 33 affected children differs significantly from equality. The reason for this deviation remains to be explained. Four of the 7 families with more than 1 affected child have had affected boys as well as affected girls in them; hence there is no evidence for partial sex linkage.

If hypophosphatasia is due to an autosomal recessive gene, all the parents of affected children are heterozygous for this gene, and, consequently, may show deviations from the homozygous normal individual. The plasma alkaline phosphatase activity was reported for 10 fathers and 12 mothers. Six (60 per cent) of the fathers, and 9 (75 per cent) of the mothers were reported to have had low levels of plasma alkaline phosphatase activity. None had any pertinent skeletal abnormalities. As far as the evidence goes, it indicates that the majority (about 70 per cent) of the heterozygotes have detectably reduced plasma alkaline phosphatase activity.

Two-thirds of the normal sibs of the patients would be expected to be heterozygotes (assuming recessive inheritance). On the basis of the data from the parents, about 70 per cent of these would be expected to show hypophosphatasia, *i.e.*, between 45 and 50 per cent. Seven healthy sibs were tested and three were reported to have had low plasma alkaline phosphatase activity.

A striking feature of the data is the uniformity of the age at onset, and of the course, among the affected children in a family. If hypophosphatasia is genetically determined, this could mean that more than one genetic locus is involved, or that a series of alleles at one locus is involved, or that internal and/or external environ-

* Two additional cases are now being studied at the Ist. Gaslini in Genoa (Prof. G. DeToni and Durand), and will be reported. The roentgenograms examined by one of us show the typical features of the childhood type of the disease.

† Children's Cancer Research Foundation, Children's Medical Center, Boston, Massachusetts.

mental factors modify the expression of the gene, or that some combination of these is involved.

In 8 families, 1 or more children were born after the first affected child. In 5 of the families, all of these children were also affected; in the sixth family, 2 affected children were followed by a normal child who, in turn, was followed by another affected child; in another family a healthy child was born after an affected child; in each of the remaining 2 families, information about the health of an infant born after an affected child is not available.

The observed high frequency of affected children among the last born could be the result of the tendency of investigators, when studying a rare disease, to report cases soon after they are diagnosed. The increased frequency may, however, be a real one. If it is, serious consideration will have to be given to the hypothesis that hypophosphatasia is caused, at least in part, by a changed intrauterine environment.

In summary, it may be said that while the data are consistent with the assumption of recessive autosomal inheritance, and that, on this assumption, many of the heterozygotes may be detected, the data do not rule out other interpretations, including one which does not involve heredity at all. More pertinent, and carefully collected, family data are necessary before any definite conclusions can be reached.

THERAPY

Growth hormone, vitamin C, thiamin, thyroid, and testosterone have been tried without significant alteration of the clinical course of the disease or the level of phosphatase in the serum.

Vitamin D in high doses has been thought to have accelerated mineral deposition at the involved sites in some instances. However, improvement was partial and never progressed toward complete healing. In evaluating therapeutic response, the tendency toward spontaneous improvement, characteristic of the disease, has also to be taken into consideration. The intensified danger of hypervitaminosis D in the presence of hypercalcemia, renal disease, or decreased urinary calcium excretion suggests extreme care in avoiding overdosage.

Craniosynostosis may have to be corrected surgically in those patients who develop definite symptoms from it.

Surgical and supportive measures for other skeletal deformities may be indicated, but delayed healing of osteotomies has been encountered (Patient 25 and 26 and Reference 7 and 17).

REPORT OF CASES

Case 1. Girl, born at term in 1951 (Fig. 1). The mother was a primipara whose Kahn test was negative and serum alkaline phosphatase 4 Bodansky units.

At birth the heart sounds were present, but the baby failed to breathe. She had short, soft and deformed extremities and a head which appeared globular and "boneless." The birth weight was 2.250 kg. and the length was 36 cm.

At autopsy, the findings were confined to the lungs and the skeleton. There was no enlargement of the parathyroid glands and no gross or microscopic abnormality of the kidneys. The lungs were completely atelectatic, both grossly and microscopically. The cranial bones each contained a small irregular ossified plaque, the remainder being represented by osteoid in a normal but immature trabecular arrangement. The long bones of both legs revealed multiple fractures of femora and tibiae and marked angulation and bowing. Similar deformities of the ribs were present. In the mid-portion of the right tibia there was an exuberant callus. The diaphyses of the bones contained ossified portions with a predominantly cancellous pattern cloaked in subperiosteal callus. No cartilage was present in the callus. Osteoid was the predominant tissue in the metaphysis, where true trabeculation was heavy and usually distorted by metaphyseal infraction and callus formation. The hypertrophic cell zone of the cartilage was irregular, contained no calcified elements (Von Kossa stain), and was more than ten times the usual thickness. The columnar arrangement of cells was distorted and large tongues of cartilage cells and uncalcified matrix reached far into the diaphysis. Similar findings were present in all bones examined.

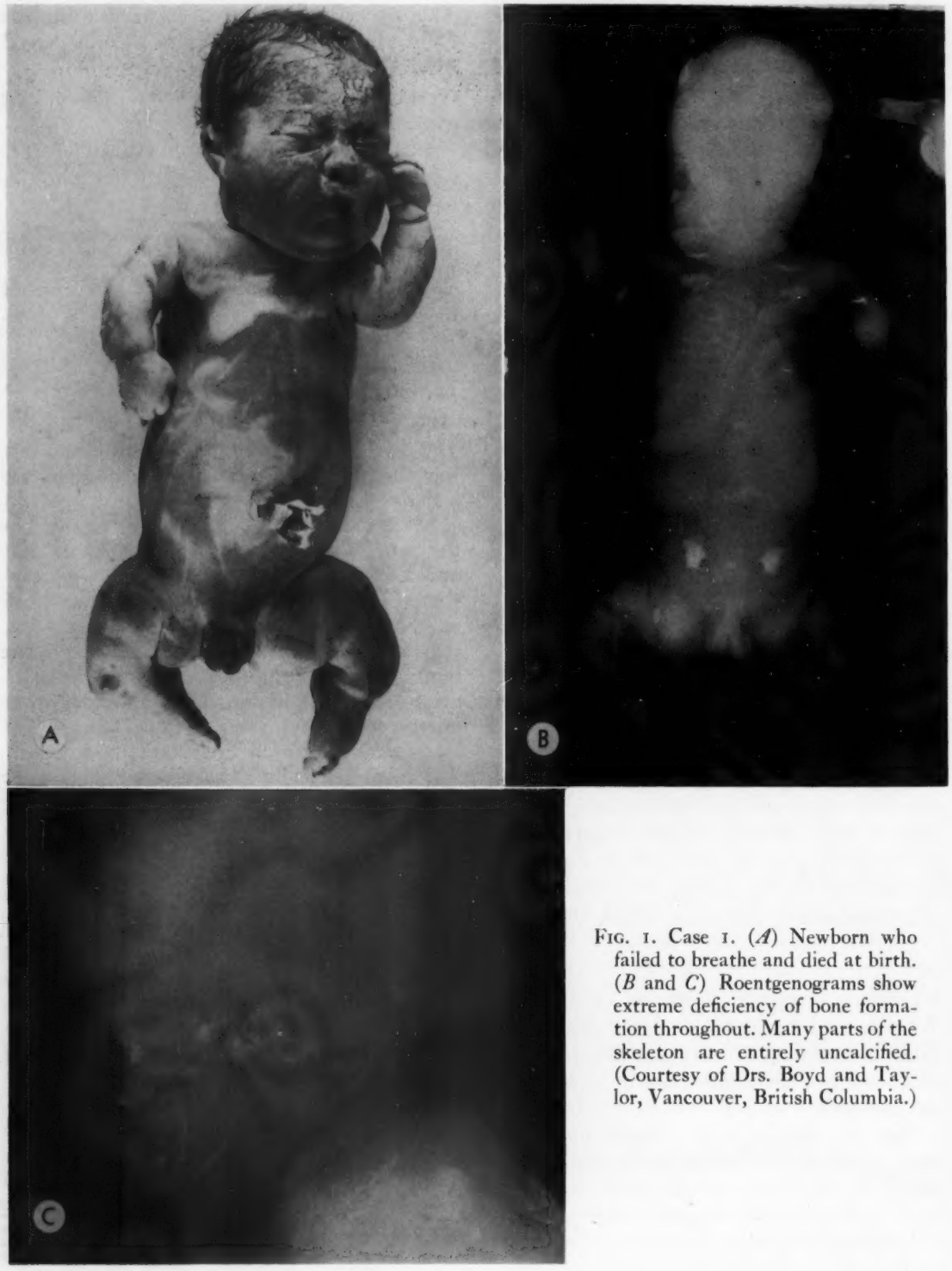


FIG. 1. Case 1. (*A*) Newborn who failed to breathe and died at birth. (*B* and *C*) Roentgenograms show extreme deficiency of bone formation throughout. Many parts of the skeleton are entirely uncalcified. (Courtesy of Drs. Boyd and Taylor, Vancouver, British Columbia.)

Fig. 2. Case 2. (*A*) Newborn who breathed poorly and died at birth. (*B* and *C*) Several parts of the skeleton, especially the skull, are entirely uncalcified. In the long bones of the lower extremities, the major changes are present in the metaphyses where there is deficient and irregular ossification. (*D*) A longitudinal section of the left femur shows angulation, shortening of the diaphysis and widened cartilage ends. (*E*) A post-mortem photograph of the cranial vault shows plaques of bone at the centers of the parietal bones. The rest is osteoid tissue. The sagittal and coronal sutures are well seen. (Courtesy of Drs. Boyd and Taylor, Vancouver, British Columbia.)

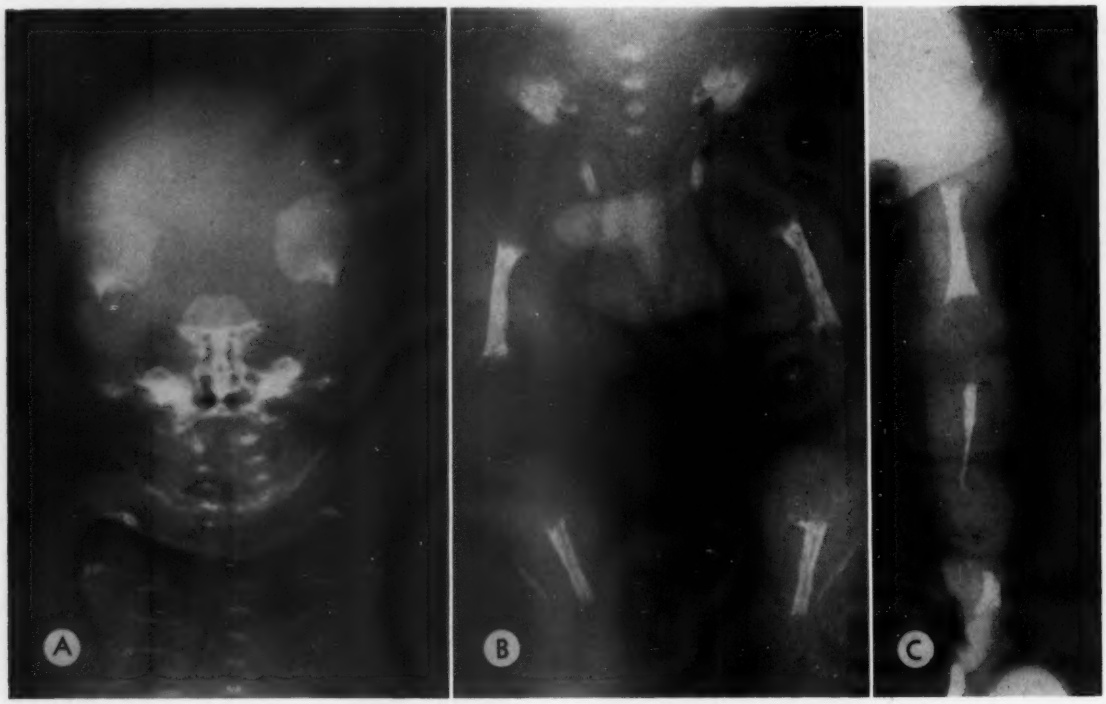


FIG. 3. Case 4. Newborn who breathed poorly and died at birth. (*A*, *B* and *C*) Note marked deficiency of bone formation throughout. (Courtesy of Dr. Arthur Childe, Winnipeg, Manitoba.)

This case is reported through the courtesy of Drs. Boyd and Taylor, Vancouver General Hospital, Vancouver, British Columbia.

CASE 2. Girl born in 1951 (Fig. 2). She was the product of a third pregnancy. The first child is alive and well, the second had a spina bifida.

Roentgenograms taken prior to delivery showed faulty skeletal ossification. The baby was born at term, breathed poorly, and died shortly after birth. The chest never expanded completely even after repeated resuscitative attempts. The head was globular and "boneless" and the extremities were short, soft and stubby. The birth weight was 3.360 kg. and the length was 45 cm.

At autopsy, the positive findings were confined to the lungs and the skeleton. No enlargement of the parathyroid glands and no gross or microscopic abnormalities of the kidneys were noted. There was bilateral pneumothorax, and extensive petechial and alveolar hemorrhages in the lungs were present. The skull was composed almost entirely of a soft tissue which on section showed osteoid trabeculae without calcification (Von Kossa stain). Only small areas of ossification in the skull were present at the centers of the anlage for these bones. All of the long bones showed similar rudimentary areas of ossification at the mid-areas of the diaphysis. The principal tissue composing the remainder of the long bones' anlage was osteoid. Many areas of bowing, fracture, callus formation and subperiosteal ossification were seen. In the callus there was no cartilaginous component, nor was there any calcification. The metaphysis, in addition to osteoid trabeculae, contained numerous tongues of hypertrophic cartilage cells often with good columnar arrangement reaching far into the diaphysis. The principal area of hypertrophic cartilage was several times wider than usual, and contained good columnar patterns. No calcified cartilage was seen. The proliferating zone of the cartilage and the indifferent cell zone of the cartilage seemed normal in pattern and extent.

This case is reported through the courtesy of Drs. Boyd and Taylor, Vancouver General Hospital, Vancouver, British Columbia.

CASE 3. Boy (Negro) born in 1929. He died shortly after birth. Roentgenograms showed the

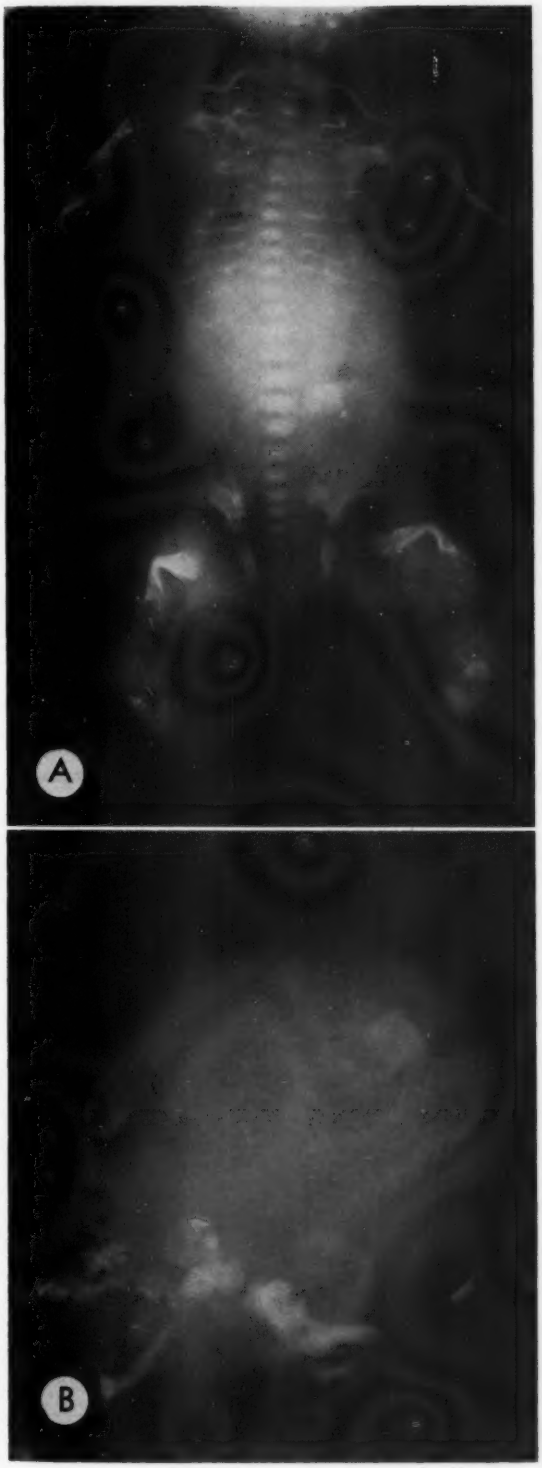


Fig. 4. Case 5. Newborn, sibling of Case 4 (Fig. 3), who breathed poorly and died at birth. (*A*) Marked deficiency and irregularity in bone formation especially in the metaphyseal regions. Note bony angulations. (*B*) Marked failure of bone formation in the skull. The roentgen changes are almost identical to those of the patient reported by Rathbun. (Courtesy of Dr. Arthur Childe, Winnipeg, Manitoba.)

lungs to be unexpanded. The entire skeleton showed changes identical to those of Case 1 and 2.

This case is reported through the courtesy of Dr. P. Riemenschneider, Syracuse Memorial Hospital, Syracuse, New York.

Case 4 and 5. Siblings born in 1952 and 1954, respectively. They had one older sibling who apparently is normal. The mother is well. Nothing is known about the father.

Case 4 (Fig. 3) was a boy born at term. He breathed poorly and died at one hour of age. The head was soft, and the extremities were short, bowed and rubbery. Postmortem examination was not performed.

Case 5 (Fig. 4) was a girl who presented a softened skull with widely separated cranial bones. The extremities were shortened and tortuous. The heart beat for fifteen minutes but the baby never breathed. The autopsy report includes no data on kidneys or bones.

These cases are reported through the courtesy of Dr. Arthur Childe, Winnipeg Children's Hospital, Winnipeg, Manitoba.

Case 6. A girl, born in 1945 (Fig. 5). The family contained 3 siblings. Father and mother are well. Their serum alkaline phosphatase levels were 0.88 and 0.66 Bessy-Lowry units, respectively. The mother's Kahn test was negative. The older sister is apparently normal, and when five years old showed a phosphatase of 2.58 Bessy-Lowry units. Another sister, born in 1950, had identical abnormalities of the skeleton to those of the patient. She gasped a few times and died shortly after birth.

S. B. was born at term. She had considerable respiratory difficulty and cyanosis. The skull was soft and the cranial bones were deficient. She was admitted to the hospital at two weeks and died at nineteen days of age.

No postmortem examination was performed.

This case is reported through the courtesy of Drs. C. R. Scott, F. N. Silverman, and E. H. Sobel.

Case 7. Reported by Rathbun.[1]

Case 8 and 9. Reported by Chown.[4]

Case 10 and 11. Reported by Kubatsch.[5]

FIG. 5. Case 6. Newborn who had respiratory difficulty and cyanosis and who died at nineteen days of life. Roentgenograms taken at two weeks showed marked irregularity and delay in bone formation, more prominent at the growing sites of all the bones. Note metaphyseal infractions. The skull was very soft on palpation. The stomach contains barium. (Courtesy of Drs. Scott, Silverman, and Sobel.)

CASE 12 and 13. Siblings born in 1944 and 1947, respectively. They have one normal older sister whose phosphatase was 4.56 Bessy-Lowry units. The father's phosphatase levels were 0.95 and 1.11 Bessy-Lowry units and the mother's were 0.59 and 0.42 Bessy-Lowry units.

Case 12, K.I.S., was born at term, weighing 3.4 kg. He did well during the first three months but never held his head up and gained only to 4.5 kg. on an adequate diet and 15 drops of vi-delta daily.

At three months of age he began to refuse feedings and became very quiet. He vomited off and on, was constipated and failed to gain weight. The cranial sutures at that time were noted to be wide and anemia was found. Roentgenograms were interpreted as showing rickets. In spite of the addition of 40 drops of oil of percomorph and iron medication to the diet, the baby failed to improve and became irritable, especially when handled. He was hospitalized for six weeks at six months of age. On admission his weight was 4.7 kg., his length 57 cm., and his head circumference 41.7 cm. The fontanelles and cranial sutures were wide. The scalp veins were prominent. There was slight costal beading. The baby was poorly developed and could not hold his head up but appeared alert. He had no teeth. The hemoglobin varied from 9 to 11 gm. per cent and the white blood cell count ranged from 12,000 to 24,000 with a normal differential. The findings in the urine were: specific gravity 1.006–1.010, albumin trace, many white blood cells, and negative cultures. The blood urea nitrogen was 24.6 mg. per cent and the urea clearance was 51 per cent of normal. The nonprotein nitrogen measured from 30 to 45 mg. per cent. The intravenous pylogram showed no excretion of contrast material up to 30 minutes. Roentgenograms showed generalized involvement of the skeleton similar to that seen in his sister. The Wassermann test was negative. In the blood serum, the calcium ranged from 10.8 to 14.8 mg. per cent, the phosphorus from 4.1 to 5.7 mg. per cent, and the phosphatase from 0.3 to 1.6 Bodansky units on four determinations.

The hospital course was characterized by unexplained febrile episodes. The blood pressure varied from 160–110 systolic and 100–70 diastolic. The child was anorexic and vomited intermittently. The anterior fontanelle became more prominent.

The baby spent the last month of his life at home. He gained to 5.8 kg., stayed awake more and was not as irritable when handled. Attacks of unexplained fever persisted. Terminally, the baby began to emit sharp cries and he died at eight months of age.

Postmortem examination was severely restricted. The body length was 57.5 cm. and there was marked shortening of all of the extremities. The weight was 5 kg. The head appeared small and both fontanelles were open and bulging, with a wide fibrous zone between the cranial bones. The only positive microscopic findings were present in the bones and the kidneys. The bones showed a rather marked deposit of osteoid in all areas examined. However, no areas of growing cartilage were available for study. Sections of the shafts of the ribs showed thick subperiosteal deposits, most of which were osteoid. The remainder of the trabeculations of the ribs was more immature than usual in this age group. No abnormalities

of the cellular elements were seen. Myeloid hyperplasia was present. In the kidneys the architecture was well preserved and only a few foci of chronic inflammatory cells were seen. A few of the tubules contained a blue staining material but most of them were empty.

Case 13, K.S. (Fig. 6), was born at full term, weighing 3.4 kg. She did well for one month and then stopped gaining on an adequate diet, including 6–10 drops of oil of percomorph a day.

At three months of age she weighed 4.3 kg. She vomited occasionally and seemed weak and hypotonic but mentally alert. The head circumference was 42 cm., and the fontanelles and cranial sutures were wide. The anterior fontanelle was bulging but not tense.

The hemoglobin measured 7.6 gm. per cent with 2.3 million red blood cells per cc. The white blood cell count ranged from 8,000 to 12,000. The urine was free of albumin but showed an occasional white blood cell. The blood urea nitrogen varied from 18 to 24.5 mg. per cent. The intravenous pyelogram was normal. The Mazzini test was negative. A ventriculogram showed no abnormality. In the blood serum, the calcium measured 12–14.7 mg. per cent, the phosphorus 4.7–5.8 mg. per cent, and the phosphatase 0.9–2.8 Bodansky units.

Roentgenograms showed generalized skeletal involvement with widening of the cranial sutures, bulging of the anterior fontanelle and marked demineralization of all the metaphyses. There was coarsening of the metaphyseal trabeculation, widening of the epiphyseal plates, but no fraying of the metaphyses.

This baby also had unexplained febrile episodes, became irritable and had two convulsions. A thoracic deformity developed. At seven months, the renal function had diminished to 4 per cent urea clearance with poor excretion by intravenous pyelography. She died at eight months of age. The immediate cause of death was aspiration. Her weight was 4.1 kg., her length 58 cm., and her head circumference 42 cm.

The gross findings at postmortem examination were not remarkable except for marked congestion and consolidation of both lungs. Microscopically, the lungs showed a marked congestion and atelectasis. The kidneys showed a few foci of chronic inflammation in the cortex and an occasional glomerulus showed hyalinization. Many distal tubules were dilated and contained hyaline and calcified casts. Calcification in the peritubular areas occasionally was seen, and interstitial round cell infiltration also occurred focally. The costochondral junctions showed marked distortion of the growth zone. The zone of proliferating cartilage cells was slightly wider than usual while the zone of hypertrophic cells was several times normal width. The cell columns could hardly be distinguished. Infraction had occurred at the junction of the hypertrophic cell zone and the metaphysis, and there was marked callus formation in this area. The metaphysis and the callus were almost completely composed of osteoid and the trabecular architecture was haphazard. The shafts of the ribs showed a more immature pattern than normally with much osteoid formation and subperiosteal ossification.

Fig. 6. Case 13. Photograph of the patient at three months of age. (Courtesy of Dr. Warren E. Wheeler, Columbus, Ohio.)

Case 12 is reported through the courtesy of Drs. A. M. Butler, and G. Reyersbach. Case 13 is reported through the courtesy of Dr. W. E. Wheeler. These patients are also mentioned as Cases 3 and 4 under "Reference No." in Table I.

Case 14. Reported by Engfeldt and Zetterstrom.[10]

Case 15. C. W. was a Negro girl, born in 1954 (Fig. 7). The parents are alive and well. The father's serum alkaline phosphatase was 1.2 Bodansky units, 1.8 Bodansky units, and 4.6 King-Armstrong units (1 KA = 1.8–3 BU). Results of the phosphatase determination on the mother were 1.7 Bodansky units, 1.8 Bodansky units, and 3.9 King-Armstrong units. An older sibling is well and had a phosphatase of 11 Bodansky units.

At birth this patient weighed 2.7 kg. and had

club feet and bow legs with pretibial skin dimples. Congenital lateral angulation of femora, tibiae, and fibulae were demonstrated roentgenographically. Vitamin D, 1,200 units daily, was started at one month of age.

She was hospitalized at four and a half months because of poor weight gain and an apparent increase in the skeletal deformities. At this time she weighed 4.1 kg. She was 50.5 cm. in length. The head circumference was 38.5 cm. and the calvarial bones were soft and small. The fontanelles were increased in size. A rachitic rosary was palpated bilaterally. The child appeared bright.

Urinalyses were normal. Hemoglobin was 13 gm. per cent. The white blood cell count was 16,000. Serum calcium, phosphorus, and alkaline phosphatase levels were respectively

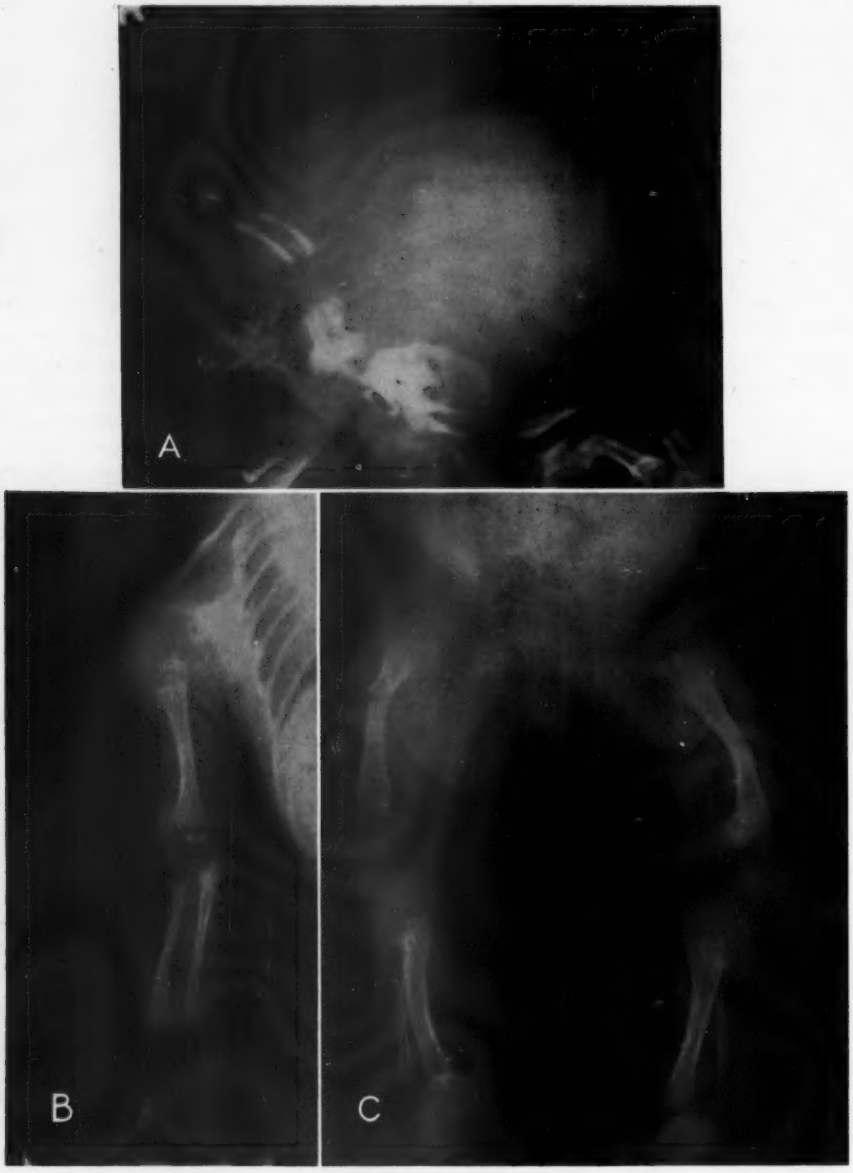


FIG. 7. Case 15. (*A*, *B* and *C*) Roentgenograms taken at four and one half months of age. The disease involved the entire skeleton. Note widening of the sutures and angulation of the bones of the lower extremities. (Courtesy of Dr. J. L. Wilson, Ann Arbor, Michigan.)

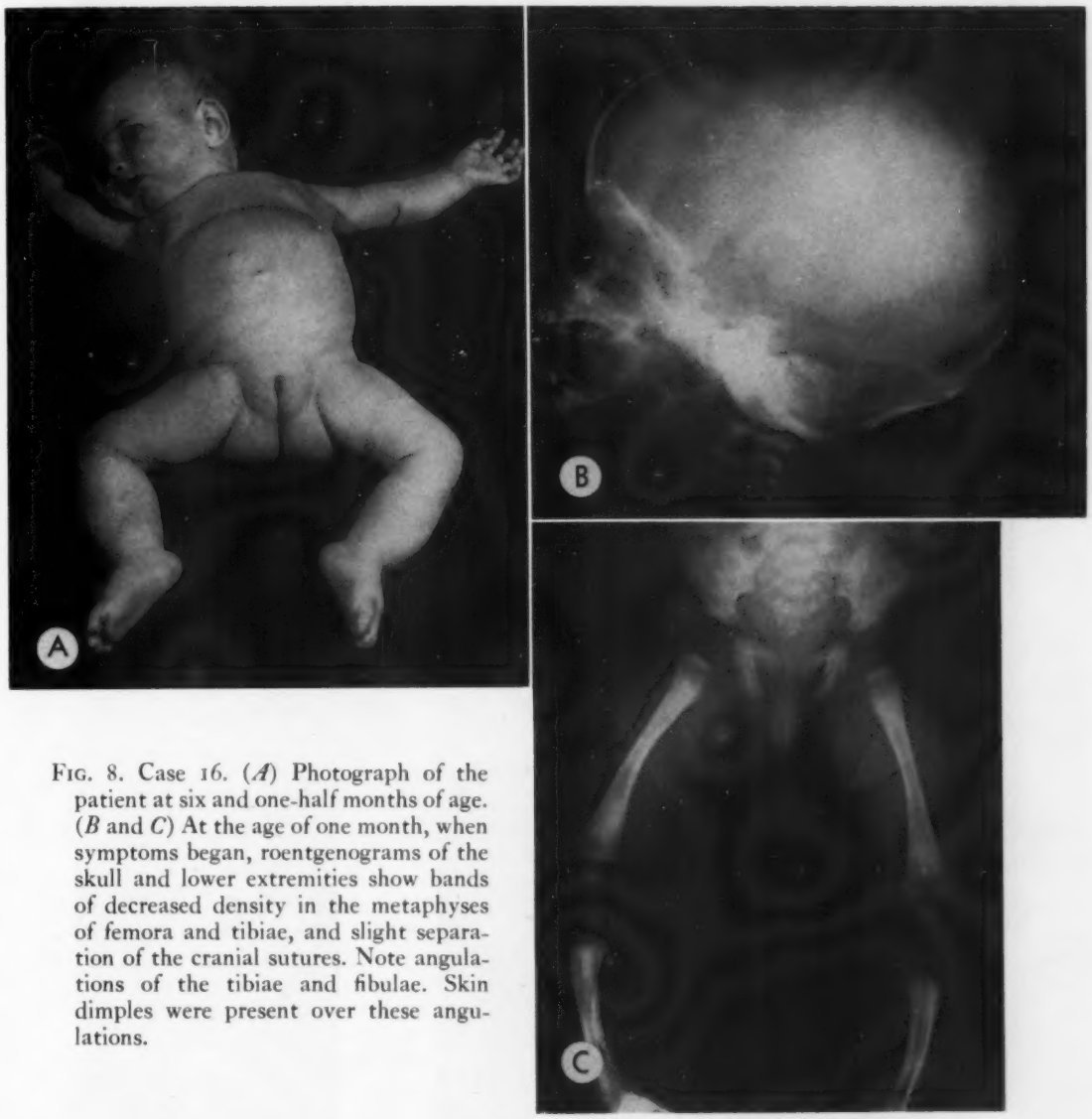


Fig. 8. Case 16. (*A*) Photograph of the patient at six and one-half months of age. (*B* and *C*) At the age of one month, when symptoms began, roentgenograms of the skull and lower extremities show bands of decreased density in the metaphyses of femora and tibiae, and slight separation of the cranial sutures. Note angulations of the tibiae and fibulae. Skin dimples were present over these angulations.

13.5 mg. per cent, 5.5 mg. per cent, and 1.2 Bodansky units. The phosphatase determination was repeated at another hospital and was 2.4 King-Armstrong units. The roentgen changes are illustrated in Figure 7.

After discharge she did poorly and at eight and a half months she weighed 3.9 kg., and measured 53 cm. with gross deformities of all extremities. She died at nine months of age.

This case is reported through the courtesy of Dr. J. L. Wilson, University Hospital, Ann Arbor, Michigan.

Case 16. This patient was born in 1953 (Fig. 8). Her parents are living and well and she has two older apparently normal siblings. The father's and mother's phosphatase levels were respectively 4.4 and 1.5 Bodansky units.

The infant was born at term and weighed 3.5 kg. She ate poorly from the start and vomited occasionally. She received 0.3 cc. of visyneral daily from birth. At one month, roentgenograms were taken because the baby tended to hold her legs in frog position. These and subsequent roentgenograms are shown in Figure 8, *B–J*. During the following five months the baby had several episodes of unexplained fever. When six and a half months old, she was hospitalized (Fig. 8, *A*). She weighed 4.8 kg. and measured 57 cm., while her head circumference was 40.5

FIG. 8. (*D*, *E*, *F* and *G*) Roentgenograms at six months of age when all the symptoms were well developed show considerable skeletal involvement at all of the growing areas. This is characterized by marked metaphyseal demineralization and diminution and irregularity of bone formation with abundance of the pre-osseous tissue. The epiphyses have a mottled sclerosis. The cranial sutures are wide and the ossification at the suture lines is irregular and mottled.

Fig. 8. (*H, I and J*) Roentgenograms taken at twenty-two months show total craniosynostosis with increased digital markings. Incomplete healing has taken place at previously involved areas. The metaphyses have a coarse architecture and there are large areas of nonossified tissue projecting into the metaphyses from the epiphyseal lines. Portions of involved epiphyseal lines are now normal in appearance. In a few bones the process has completely subsided.

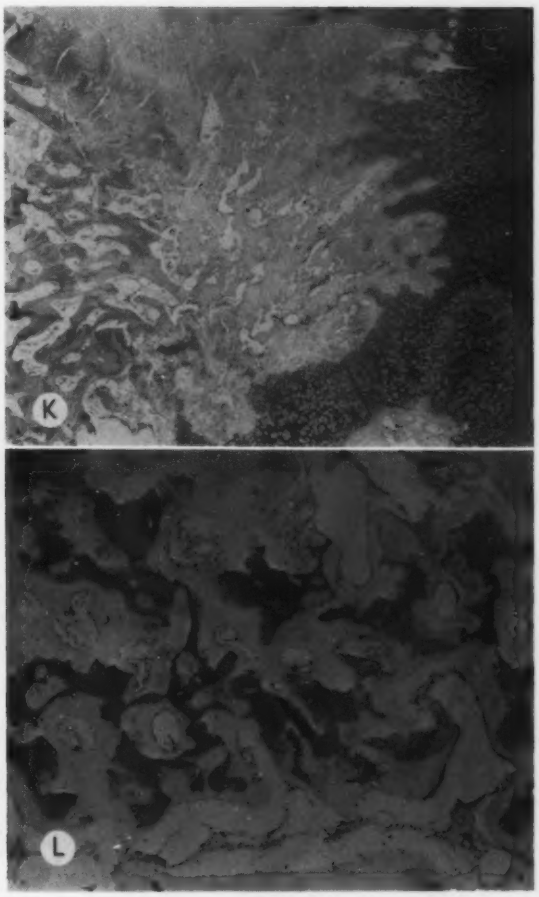


Fig. 8. (*K*) Biopsy of a costochrondral junction at six months shows slight widening of proliferating cell zone and marked irregularity and enlargement of hypertrophic cell zone of cartilage and interlacing thickened trabeculae of osteoid in the metaphyses. (*L*) Special stain for calcium (black) made on undecalcified bone shows wide osteoid borders and irregularly calcified cores in the trabeculae.

cm. She could not hold her head up or sit. No teeth had erupted. She appeared alert. The anterior fontanelle measured 5 by 5 cm. and bulged but was not tense. The cranial sutures were widely separated. A rachitic rosary was present and the wrists and ankles were enlarged. There was some sternal retraction in inspiration. She was hypotonic and skin dimples were present over the lateral aspects of each lower leg at the site of a definite bony prominence. Her blood pressure was 110/80.

The hemoglobin was 11 gm. per cent, the white blood cell count varied from 25,000 to 8,000 with a normal differential. The urine specific gravity ranged from 1.005 to 1.015 and of 8 specimens 3 contained a trace of albumin with occasional white blood cells. The Sulkowitch test was one plus. The nonprotein nitrogen ranged from 26 to 36 mg. per cent. The intravenous pyelogram showed good concentration and normal structures. The Hinton test was negative. Liver function tests were normal. In the blood serum the calcium was 9.5–12 mg. per cent, the phosphorus 3.4–3.0 mg. per cent, the phosphatase 0.75–1 Bodansky units, and the total protein 6.1 gm. per cent. She had episodes of unexplained fever, was irritable and disliked being handled. She gained 180 gm. in a month.

Biopsy of the costochondral junction showed

grossly a marked softening of all of the bony and cartilaginous structures with a very wide cupping at the metaphyseal area. Histologically (Fig. 8, *K* and *L*), the costocartilage appeared normal in the sternal portion, but at the costochondral junction the zone of proliferated cartilage was considerably wider than normal and the zone of hypertrophic cells was many times normal in width. The arrangement of columns was grossly distorted so that no columnar pattern was visible. The hypertrophic cells were irregularly patterned and little matrix was present, all of it uncalcified. Long tongues of cartilage cells penetrated into the metaphysis. This area was almost entirely composed of osteoid with wide trabeculae coursing principally in a direction perpendicular to the axis. Further into the diaphysis of the rib, small areas of calcification could be seen in the center of the osteoid trabeculae. No cortical bone was present. No evidence of fracture could be seen. Stains for alkaline phosphatase activity in this area were uniformly negative. Chemical determinations of phosphatase from cartilage, metaphysis, and diaphysis of the rib revealed no phosphatase activity determinable in these sites, while a normal control showed 4 to 6 units of activity in 100 mg. net weight. Determinations of the phosphorus and the calcium content on the specimen were also attempted and wide variations were found depending on the sampling. In the most ossified area, the ash weight of a sample which weighed 22 mg. was 0.9 mg. and in this sample phosphorus content was 0.099 mg.

After discharge from the hospital, the baby did poorly for a few months and then gradually improved. She received no treatment. Trivisol in the amount of 0.33 cc. was given daily. At the age of twenty-two months, the child was unable to walk but could crawl. She had knock knees. Her deciduous incisors were normal. She ate well and could talk in sentences. There was a bony ridge along the sagittal suture. The optic fundi appeared normal.

This case is reported through the courtesy of Drs. C. A. Janeway, and M. M. Osborne, the Children's Medical Center, Boston, Massachusetts, Record number 411105.

CASE 17. Reported by Schlesinger *et al.*[13a] (Case 1).

CASE 18. To be reported. This case is included through the courtesy of Drs. McIntosh, Caffey, Scaglione, and Lucey, Babies Hospital, New York City.

CASE 19. Reported by McCance *et al.*[11]

CASE 20. Reported by Fraser *et al.*[12a]

CASE 21. Reported by Schlesinger *et al.*[13a] (Case 2).

CASE 22. Reported by Anspach and Clifton.[6]

CASE 23. P. F. was born in 1950 (Fig. 9). Both parents were well. The father's alkaline phosphatase was 1.4 Bodansky units and 0.51 Bessy-Lowry units. The mother's phosphatase was less than 1 Bodansky unit and 0.77 Bessy-Lowry units. There were no siblings.

At birth the only abnormality noted was club

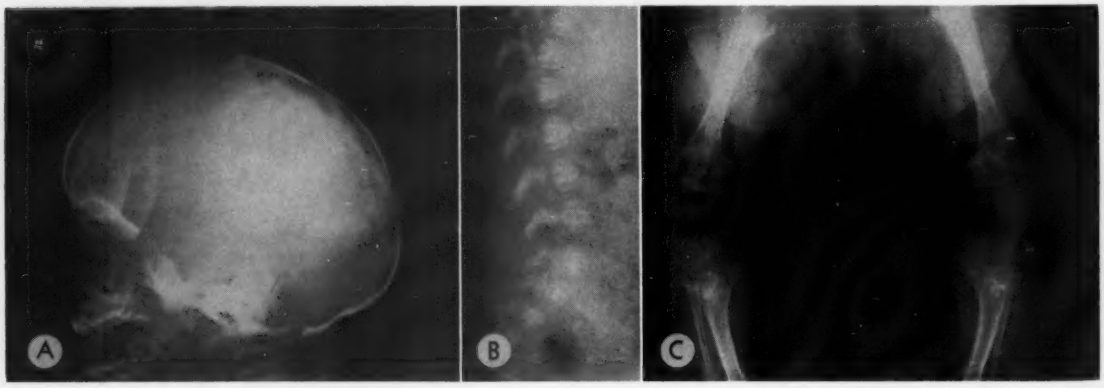


FIG. 9. Case 23. (*A*, *B* and *C*) Onset of symptoms at approximately six months of age. Roentgenograms taken at six and one-half months of age show marked generalized skeletal involvement consisting of delayed and irregular bone formation. Note metaphyseal infractions, bulging of the anterior fontanelle and separation of the sutures.

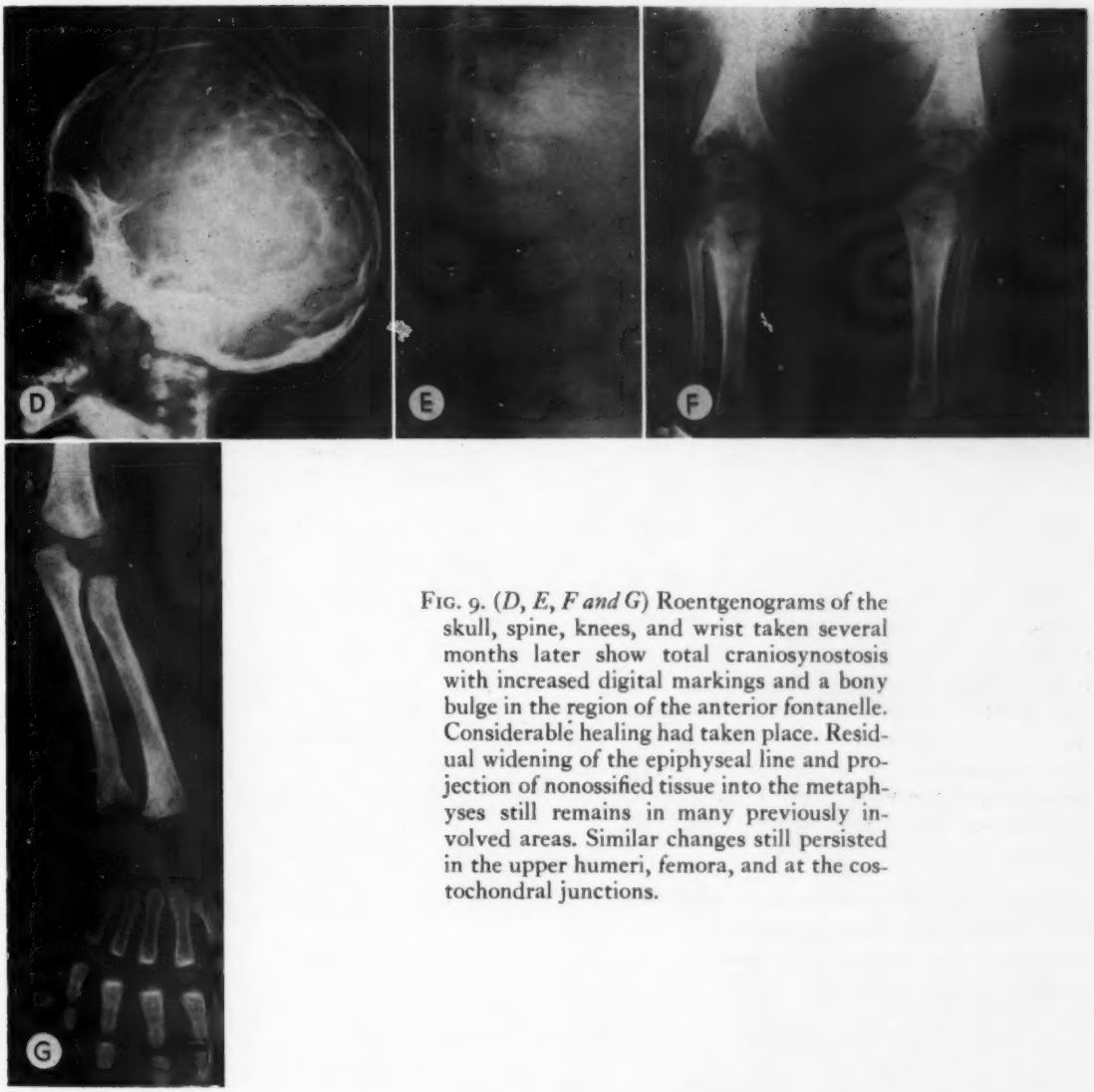


Fig. 9. (*D, E, F and G*) Roentgenograms of the skull, spine, knees, and wrist taken several months later show total craniosynostosis with increased digital markings and a bony bulge in the region of the anterior fontanelle. Considerable healing had taken place. Residual widening of the epiphyseal line and projection of nonossified tissue into the metaphyses still remains in many previously involved areas. Similar changes still persisted in the upper humeri, femora, and at the costochondral junctions.

feet. She did well until, at six months of age, she became irritable and her fontanelle bulged. She then weighed 6.250 kg. and measurements were considered normal for her age. She was hypotonic, could not sit up and appeared irritable when handled. The anterior fontanelle was prominent and tense.

The urinalyses were essentially normal. A moderate anemia was present; the white blood cell count was normal, the blood urea nitrogen was 25 mg. per cent, the Wassermann test was negative. The blood serum calcium was 10.5 mg. per cent, phosphorus was 3.1 and 4.6 mg. per cent, alkaline phosphatase 1 Bodansky unit. An intravenous pyelogram showed no abnormality. A bone marrow aspiration was interpreted as showing some myeloid hyperplasia. Subdural and ventricular taps and a ventriculogram were normal.

The child was treated with 1,500 to 5,000 units of vitamin D for seven months. During this period the serum calcium remained within normal limits and the phosphatase continued to be low (0.4 to 1 Bodansky unit). Some improvement was noted both clinically and roentgenographically. The child lost 2 incisors before she was two years old.

From the age of fourteen to twenty-two months, she was given 50,000 units of vitamin D daily. A weekly Sulkowitch test remained normal. Vitamin D therapy was discontinued when the serum calcium rose to 14.4 mg. per

cent. At that time there was roentgen evidence of diffuse extraskeletal calcification. During the ensuing months, up to the time of death at two years and five months, the course was downhill. The phosphatase values continued to be low. Nonprotein nitrogen and serum phosphorus became elevated terminally.

A rib biopsy performed at seven months of age was reported as showing findings compatible with rickets. The autopsy in addition revealed "calcifications of kidneys, heart, and tentorium and evidence of interstitial left nephritis." The roentgen changes are illustrated in Figure 9.

This case is reported through the courtesy of Dr. L. Luzzatti, Stanford University Hospital, San Francisco, California.

CASE 24. Reported by Schlesinger *et al.*[13a] (Case 3).

CASE 25 and 26. These are two brothers who were admitted to the Cleveland Clinic in 1949 at the age of thirteen and ten years, respectively, for surgical correction of knock knees. The parents are alive and well. Another sibling was born in 1955 and is now three months old. No information is available on him. The father's and mother's serum alkaline phosphatase levels were respectively 1.8 and 2.8 Bodansky units.

Case 25, J. H., was born in 1936. He had been knock-kneed since he started to walk and had had some difficulty in walking. The deciduous dentition was normal. On admission at thirteen years of age, the laboratory findings showed the following: urinalysis and hemogram normal, serum calcium 14–19 mg. per cent, serum phosphorus 5.7 mg. per cent, alkaline phosphatase 0.7 Bodansky units, blood urea nitrogen 24 mg. per cent, normal intravenous pyelogram and urea clearance. The Kahn test was negative. The osteotomies healed slowly.

When re-examined in 1955 at the age of nineteen, he appeared well. His head, however, is described as being "curiously shaped" but without other gross clinical abnormality. Serum calcium was 11 mg. per cent, phosphorus 3.2 mg. per cent and alkaline phosphatase 0.22 Bodansky units, serum protein 7.8 mg. per cent.

Case 26, R. H., was born in 1938. Like his brother, he had had knock knees since he started to walk. He was wearing supportive braces at four. He lost his deciduous teeth at three and a half to four years. When seen at ten years, the clinical laboratory findings were practically identical to those presented by his brother on admission. The serum alkaline phosphatase was less than 1 Bodansky unit and the osteotomies likewise healed slowly.

At thirteen years of age, the serum calcium was found to be 10.4 mg. per cent with a phosphorus of 3.6 mg. per cent, and alkaline phosphatase of 4.3 Bodansky units.

When re-examined at seventeen years of age, the legs were short and the head had the same appearance as his brother's. The laboratory findings at this time showed a normal hemogram and urinalysis, a serum calcium of 11.2 mg. per cent, phosphorus 4.23 mg. per cent, alkaline phosphatase 0.39 Bodansky units, and a blood urea nitrogen of 24 mg. per cent with a normal urea clearance.

The original roentgenograms of the skeleton at the age of ten years (Fig. 10) showed exactly the same changes as those of his brother. Slight improvement took place in the following years. At seventeen, the trabecular architecture of all the previously involved metaphyses was coarse and mottled and small irregular radiolucent areas were still present in the distal metaphyses of the radius and ulna in the femoral necks at the base of the greater trochanters and at the knees. The epiphyses were fused.

These cases are reported through the courtesy of Drs. R. W. Schneider and A. C. Corcoran who have presented an abstract of them.[8]

CASE 27. G.S., born in 1948, is now six years and nine months of age. Her general health is only fair, as she has frequent respiratory tract infections. There have been several one-hour episodes of heart pounding, sweating, pallor and dyspnea; their nature has not yet been established. Her height and weight continue to be at the third percentile. She has knock knees and slight enlargement of the wrists. The thoracic deformity has increased. The head is normal. Two of the remaining deciduous molars have been shed and 3 six-year molars have emerged. No cuspid or incisor teeth are present. The mucosa of the tongue is still patchily irregular. The heart and lungs are normal on physical examination. The liver is distinctly enlarged but is not tender. The roentgenograms demonstrate very slow improvement. Her serum alkaline phosphatase activity continues to be abnormally low. There are no siblings. Dr. Dent has recently found phosphoethanolamine in her urine.

Fig. 10. Case 25. (*A*, *B* and *C*) Mild symptoms present in early childhood. The first roentgenograms were taken at ten years of age. These showed that almost all the growing areas of the skeleton were involved. Defective ossification in the femoral necks, in the metaphyses at the knees and upper humeri, evidently of long-standing. Irregular areas of uncalcified preosseous tissue left behind in the growth process. Note scalloping of the iliac crests and scapulae. Roentgenograms taken at seventeen years of age showed that all the epiphyseal lines were closed. The iliac crests were apparently normal. Small radiolucent areas remained in the previously involved metaphyses.

This case is reported through the courtesy of Drs. Sobel, Clark, Fox, and Robinow.[9a]

Case 28. M.R. was born in 1949. The parents are apparently normal. The mother's serum alkaline phosphatase was 0.66 Bodansky units. An older brother was normal, and had a serum alkaline phosphatase of 3.3 Bodansky units.

M.R. was a "feeding problem" in the first months of life but subsequently did well. He was prescribed daily vitamin D. He started to walk at sixteen months. At eighteen months of age, the deciduous incisors became loose and then fell out. He was noted to be irritable and cried when handled.

On admission at twenty months of age, there was a rachitic rosary but no enlargement of the bone ends; the legs were straight, and the patient walked without pain. The head was not remarkable. The blood pressure was normal. The hemogram was normal. The urinalysis was normal. The nonprotein nitrogen was 45 and 36 mg. per cent on two separate occasions. A urea clearance was 86 per cent. In the serum, the total protein was normal, the calcium 10.2 and 9.5 mg. per cent, the phosphorus 5.9 and 4.8 mg. per cent. The alkaline phosphatase on four determinations ranged from 0.2 to 0.7 Bodansky units.

Two years later the child was apparently

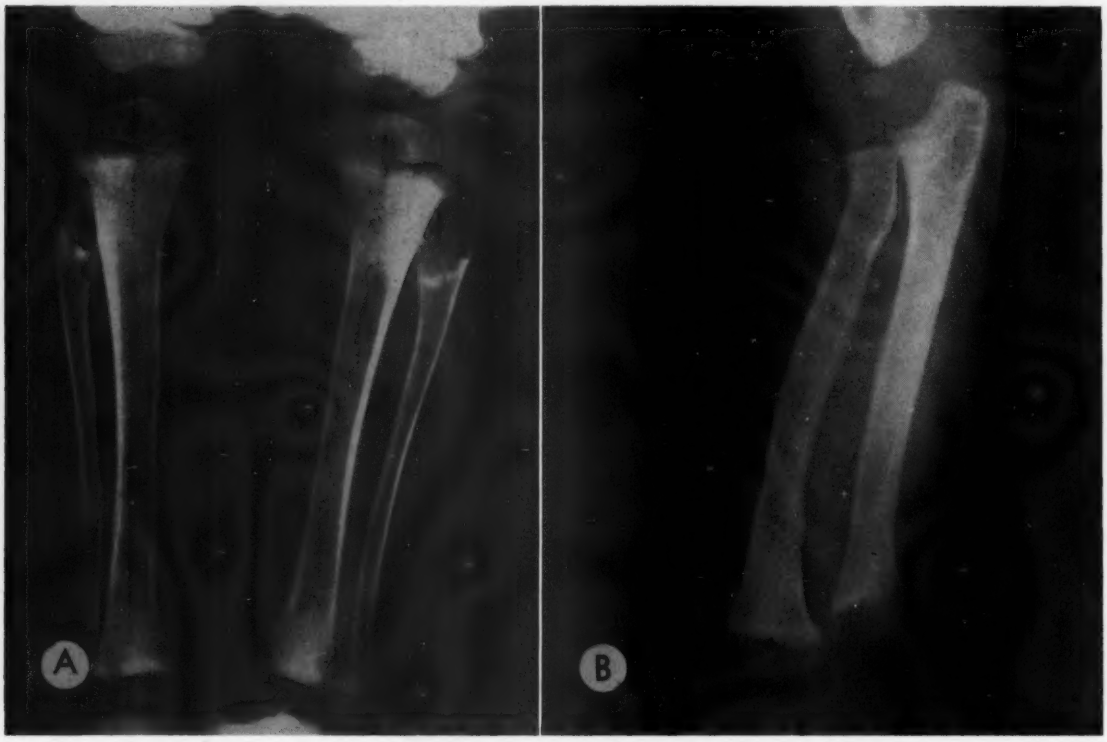


FIG. 11. Case 28. (*A* and *B*) Onset of symptoms at approximately sixteen months of age. Roentgenograms taken at twenty months show involvement of the proximal ends of the fibulae and distal ends of the ulnae. Other involved areas were the upper ends of the humeri and costochondral junctions. The skull was normal. Note alteration of the architecture in the metaphyses of both tibiae, indicating that disease must have been present longer than suspected from the history. (Patient of Dr. F. N. Silverman.)

well except for mild skeletal deformities and further loss of teeth. The roentgen findings are illustrated in Figure 11.

This case is mentioned in Reference 9a (Case 2) and we are indebted to the authors and Dr. F. N. Silverman for additional data.

CASE 29, 30 and 31. These are two sisters and a brother. They have a sister who has no skeletal abnormalities and who has a serum alkaline phosphatase determination of 10 Bodansky units and 3.04 Bessy-Lowry units. The parents are living and well. The level of alkaline phosphatase in their serum is not known.

Case 29, S.S., was born in 1943. The first symptom was loosening of the newly emerged incisors between eight and ten months of age. Roentgenograms of the long bones at one year showed fairly well developed rickets, in spite of the fact that she has been getting 10 drops of oil of percomorph daily since the age of two weeks. Following the discovery of rickets, vitamin D administration was increased to 30 drops of oil of percomorph, and 15 drops of vi-penta. No improvement was noted on this therapy. In addition, the child ate poorly and developed bone pains and knock knees which made it difficult for her to walk.

At the age of two years, she presented genu valgum and had a waddling gait. The anterior fontanelle measured 2.5 by 2.0 cm. The incisors were missing. Laboratory findings included a normal hemogram; urinalysis showed a specific gravity between 1.005 and 1.028, and occasional red and white blood cells. Urine cultures showed no growth. Blood urea nitrogen, nonprotein nitrogen and urea clearance were normal. Intravenous and retrograde pyelograms were not remarkable. The stools showed no excessive fat. In the blood serum, the calcium ranged from 10.1 to 10.9 mg. per cent, the phosphorus from 4.9 to to 5.7 mg. per cent and the phosphatase from 3.2 to 4.7 Bodansky units.

The patient was treated with splints to her

Fig. 12. Case 29. (*A*, *B* and *C*) Onset of symptoms between eight and ten months of age. Roentgenograms of the pelvis, knees and left hand at two years showed mild involvement of the metaphyses with irregular bone formation and areas of non-osseous tissue projecting into diaphyses. Note scalloping of the iliac crests and residual uncalcified areas in the metaphyses.

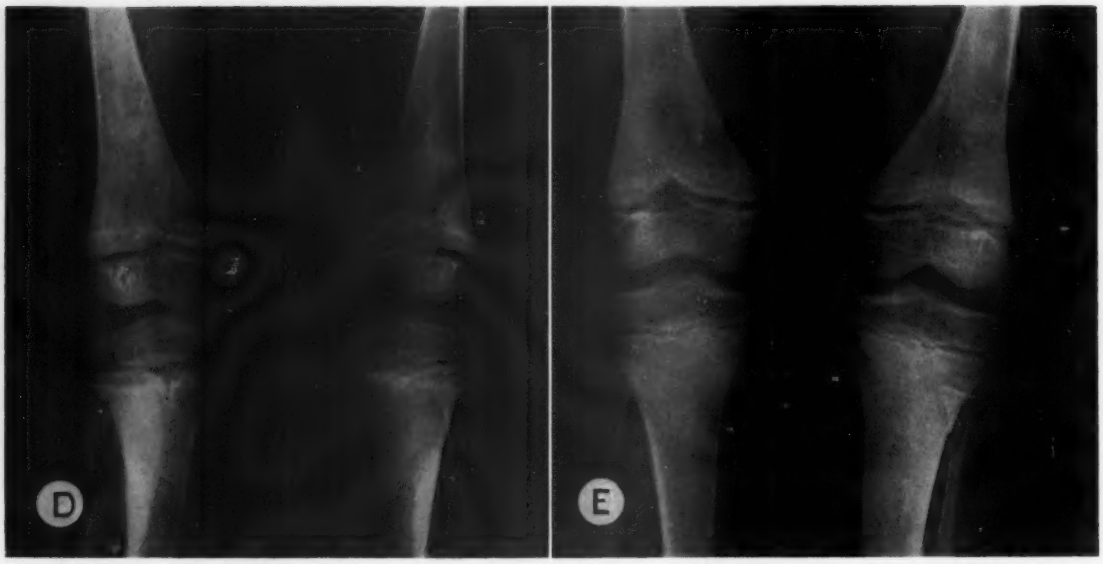


FIG. 12. (*D* and *E*) Knees at four and eight and one-half years, respectively, show only minimal improvement. The skull and many other parts of the skeleton were normal.

legs, calcium gluconate, and ertron 500,000 units i.m. daily for the month she spent in the hospital. This appeared to result in some improvement and she was sent home on 100,000 units of vitamin D by mouth daily. Repeat chemistries done two months after the beginning of this therapy showed no change in the serum calcium and phosphorus levels. The phosphatase was 1.6 and 7.6 Bodansky units. The kidney function remained normal. Signs of vitamin D intoxication with a calcium of 14.4 mg. per cent appeared after three months and the vitamin was discontinued.

The child was last seen at the age of eight and a half years in 1951. At that time she was 121.5 cm. long and weighed 23 kg. She still had marked knock knees and beading of the costochondral junctions. The permanent incisors had emerged and appeared normal as did the six-year molars. The phosphatase was still low, 0.83 Bessy-Lowry units, the serum calcium was within normal limits and the phsphorus 6 mg. per cent. The roentgen changes are illustrated in Figure 12.

Case 30, E.S., was born in 1944. Cod liver oil had been given since two weeks of age. The first teeth appeared at five months. The incisors became loose shortly after emerging and were lost between fifteen and eighteen months of age. The legs were straight at the age of thirteen months but a rosary was present and wrists and ankles were broad. When last seen at the age of six and a half years, the child was 116 cm. in height and weighed 20.5 kg. She had 6 normal permanent incisors. At that time she had definite knock knee deformity. The blood calcium was 8.2 mg. per cent, the phosphorus 6.3 mg. per cent and the alkaline phosphatase 10.8 Jenner-Kay (modified Bodansky) units, but this value was not checked. The roentgen changes are similar to but milder than those of Patient 29.

Case 31, D.S., was born in 1949. He had also been given "adequate" amounts of vitamin D since the age of two weeks. At eighteen months of age, he began to shed his lower and upper incisors. When seen at the age of two and a half years, he weighed 13 kg. and was 89½ cm. in height. The wrists were thick. There was flaring of the lower ribs and knock knees. The calcium was 8.4 mg. per cent, the phosphorus 7.2 mg. per cent and the phosphatase 5.3 Jenner-Kay (modified Bodansky) units. The roentgen changes are similar to but milder than those in Patient 29.

These cases are reported through the courtesy of Drs. S. W. Clausen,* W. Bradford and L. F. Squire; mentioned as Patient 6, and her two siblings are discussed in Reference 9a.

CASE 32. Reported by Hühne and Schönfeld.[2] Changes similar to Rickabaugh but slightly more prominent.

CASE 33. Reported by Illingworth and Gardiner.[14]

* Deceased.

SUMMARY

Hypercalcemia is a rare chronic disorder characterized by deficient bone formation, histologic changes resembling rickets and low phosphatase activity of serum, bones and other tissues. Other less constant features are defective ossification of the skull in early life with subsequent development of premature craniosynostosis, premature loss of deciduous teeth, hypercalcemia, and urinary and renal function abnormalities. The disease may occur in siblings, and one or both parents often show a low serum phosphatase without evidence of bone disease.

From the review of the literature and information on several unpublished cases, a total of 33 instances has been collected.

The clinical and roentgenologic features of the disease vary greatly in different age groups of childhood and an attempt has been made to describe these variations.

The etiology of the disease is unknown, but a genetic abnormality seems probable.

E. B. D. Neuhauser, M.D.
The Children's Medical Center
300 Longwood Avenue
Boston 15, Massachusetts

REFERENCES

1. Rathbun, J. C. "Hypophosphatasia," new developmental anomaly. *Am. J. Dis. Child.*, 1948, *75*, 822–831.
2. Hühne, T., and Schönfeld, E. Eine eigenartige Wachstumsstörung im Kindesalter. *Monatschr. f. Kinderh.*, 1928, *42*, 267–286.
3. Parenti, G. C. La anosteogenesis (una varietà della osteogenesi imperfetta). *Pathologica*, 1936, *28*, 447–461.
4. Chown, B. Renal rickets and dwarfism: pituitary disease. *Brit. J. Surg.*, 1936, *23*, 552–566.
5. Kubatsch, H. Über eine seltene Knochenerkrankung. *Monatschr. f. Kinderh.*, 1938, *75*, 253–263.
6. Anspach, W. E., and Clifton, W. M. Hyperparathyroidism in children; report of two cases. *Am. J. Dis. Child.*, 1939, *58*, 540–557.
7. Macey, H. B. Multiple pseudofractures: report of case. *Proc. Staff Meet., Mayo Clinic*, 1940, *15*, 789–791.
8. Schneider, R. W., and Corcoran, A. C. Familial nephrogenic osteopathy due to excessive tubular reabsorption of inorganic phosphate: New syndrome and novel mode of relief, *J. Lab. & Clin. Med.*, 1950, *36*, 985–986.
9. a. Sobel, E. H., Clark, L. C., Jr., Fox, R. P., and Robinow, M. Rickets, deficiency of "alkaline" phosphatase activity and premature loss of teeth in childhood. *Pediatrics*, 1953, *11*, 309–321.
   b. Sobel, E. H., Clark, L. C., Jr., and Robinow, M. Report on disorder of skeleton resembling rickets, associated with loss of teeth and deficient alkaline phosphatase activity in a 2 year old child. *Am. J. Dis. Child.*, 1952, *83*, 410–411.
10. Engfeldt, B., and Zetterström, R. Osteodysmetamorphosis fetalis; clinical-pathological study of congenital skeletal disease with retarded growth, hypophosphatasemia and renal damage. *J. Pediat.*, 1954, *45*, 125–140.
11. McCance, R. A., Morrison, A. B., and Dent, C. E. Excretion of phosphoethanolamine and hypophosphatasia. *Lancet*, 1955, *1*, 131.
12. a. Fraser, D., Yendt, E. R., and Christie, F. H. E. Metabolic abnormalities in hypophosphatasia. *Lancet*, 1955, *1*, 286.
   b. Fraser, D., and Yendt, E. R. Metabolic abnormalities in hypophosphatasia. *Am. J. Dis. Child.*, 1955, *90*, 552–553.
13. a. Schlesinger, B., Luder, J., and Bodian, M. Rickets with alkaline phosphatase deficiency: an osteoblastic dysplasia. *Arch. Dis. Child.*, 1955, *30*, 265–276.
   b. Schlesinger, B., Luder, J., and Bodian M. Rickets with alkaline phosphatase deficiency. *Am. J. Dis. Child.*, 1955, *90*, 605.
   c. Luder, J., and Schlesinger, B. E. Osteodystrophy due to congenital deficiency of phosphatase. *Proc. Roy. Soc. Med.*, 1954, *47*, 541–543.
14. Illingworth, R. S., and Gardiner, J. H. Premature loss of deciduous teeth. *Arch. Dis. Child.*, 1955, *30*, 449–452.
15. Lanman, J. T. Hypophosphatasia—newly recognized disease. *J. Pediat.*, 1955, *47*, 509–513.
16. Henneman, P. H., and Albright, F. By permission.
17. Frazer, D. Personal communication.
18. Neuhauser, E. B. D., and Currarino, H. Hypophosphatasia. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1954, *72*, 875.
19. Jansen, M. Über atypische Chondrodystrophie (Achondroplasie) und über eine noch nicht beschriebene angeborene Wachstumsstörung des Knochensystems: Metaphysäre Dysostosis. *Ztschr. f. orthop. Chir.*, 1934, *61*, 253–286.
20. Cameron, J. A. P., Young, W. P., and Sissons, H. A. Metaphysical dysostosis; report of case. *J. Bone & Joint Surg.*, 1954, *36B*, 622–629.
21. Fisher, O. D., and Neill, D. W. Excretion of ethanolaminephosphoric acid in coeliac disease. *Lancet*, 1955, *1*, 334–335.

NEUROBLASTOMA: A ROENTGENOLOGIC AND PATHOLOGIC STUDY*

By OWINGS W. KINCAID, M.D., *and* JOHN R. HODGSON, M.D.
Section of Roentgenology
and
MALCOLM B. DOCKERTY, M.D.
Section of Surgical Pathology
Mayo Clinic and Mayo Foundation†
ROCHESTER, MINNESOTA

NEUROBLASTOMA has long been recognized as one of the major hazards to life in childhood. Although this tumor is encountered occasionally in adults, it is predominantly a tumor of young children and is, next to leukemia, perhaps the most common malignant disease occurring in infancy and childhood. Until recent years the prognosis in all cases of neuroblastoma was generally regarded as hopeless, and interest in this condition was limited to studies of its pathology and natural history. With advances in surgery and roentgenology there is now good reason for optimism in some cases, and emphasis has been shifted to diagnosis and treatment.

The roentgenologic examination is an important clinical tool in the study of patients who may be harboring a neuroblastoma. A review of the world literature reveals that although much has been written on this disease, few studies of its roentgenologic manifestations have been made. Because of the relative infrequency with which this tumor is encountered, only two or three of these studies have been based on any large number of personally observed cases. The moment seems opportune, therefore, for the presentation of our findings in 32 cases.

HISTORICAL REVIEW

Neuroblastomas are highly malignant tumors arising from the undifferentiated, immature neural tissue of the developing sympathetic nervous system. For many years these tumors were thought to be sarcomas. Virchow[46] in 1864 was the first to recognize their neurogenic nature, but he classified them as gliomas. Marchand[34] in 1891 was probably the first to suggest that they took origin from the anlage of the sympathetic nervous system. In spite of Marchand's observations, the confusion concerning these tumors persisted, and pathologists of that day continued to refer to them as round cell sarcomas or gliomas. It was not until Wright's[50] important paper appeared in 1910 that their true nature became widely known. Wright established conclusively their neuroblastic relationship by demonstrating the similar morphology and staining characteristics of these tumors and the cells and fibrils of the sympathetic nervous system. It was he who introduced the term "neuroblastoma."

The first comprehensive reviews of the subject of neuroblastoma were published by Dunn[14] in 1915 and Lehman[29] in 1917. Since that time many papers have appeared in the literature. One of the most notable contributions is that of Farber,[15] who in 1940 reported his observations on 40 patients seen among 301 patients with malignant tumors at the Boston Children's Hospital. Ten of the 40 patients were alive and well from three to five years after operative discovery of the tumor. Thus Farber's paper dissipated the previously general acceptance of the idea that the prognosis in all cases of neuroblastoma was hopeless. Farber's optimism concerning the results of surgical and roentgen treatment

* Abridgment of thesis submitted by Dr. Kincaid to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Radiology.

† The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

of neuroblastoma was substantiated by the reports of Wyatt and Farber[51] in 1941 and Wittenborg[49] in 1950.

The roentgenographic manifestations of neuroblastoma have been described by Wyatt and Farber[51] and by Sherman and Leaming;[44] these two studies were the only ones in the roentgenologic literature based on any large number of personally observed patients.

PRESENT STUDY

The present study is based on the findings in 32 cases of neuroblastoma encountered at the Mayo Clinic in the ten years from 1945 through 1954. The files of the clinic were searched and the clinical and pathologic material reviewed in all cases in which the diagnosis of neuroblastoma had been suggested during this period. From this group 32 cases were selected in which the histologic diagnosis of neuroblastoma could be made with absolute certainty and in which roentgenograms were available for study. Although roentgenologic survey of all possible regions of involvement was not done in every case, the roentgenologic studies were felt to be generally adequate.

Retinoblastomas have been classified as neuroblastomas by some authors, but others have considered them as different tumors. Because this question is still unsettled, we did not include cases of retinoblastoma in this study.

CLINICAL FEATURES

Age, Sex and Familial Incidence. The ages of patients with neuroblastoma as reported in the literature have ranged from that of the unborn fetus to a person seventy-six years old. A few cases of fetal dystocia due to this tumor have been reported; in some, morcellation was required for delivery.[19,31,41] Several instances have been reported too in which metastasis had occurred in the newborn.[4,28,47] About 40 cases have been reported in adults so far as we could determine, but neuroblastoma is predominantly a tumor of infants and young children.

The youngest patient in our series was one month old; the oldest seventy years. The average age was 7.8 years, and the median age was 3.5 years. Twenty-one of the 32 patients were less than six years of age. Two of the patients were adults.

Neuroblastoma affects males and females with equal frequency, and there is no particular racial or familial tendency. Nineteen (59 per cent) of our patients were males and 13 (41 per cent) were females. The only instance of familial occurrence of this tumor recorded in the literature so far as we could determine is that of Dodge and Benner,[13] who encountered neuroblastomas in a brother and sister. In the 3 cases on record in which one twin was affected, the co-twin in each instance was normal.[6]

Symptoms and Signs. Presenting symptoms were commonly abdominal pain, abdominal mass, fever, debility, anorexia and bone pain. Less often, symptoms were referable to the thorax, eye, peripheral lymph nodes, subcutaneous nodules or to the spinal cord. The average duration of symptoms from the time of onset until the patient was first seen by us was 4.3 months.

The most frequently encountered abnormal physical finding was an abdominal mass. This was present in 22 (69 per cent) of the patients. In 5 of these the mass was evidently an enlarged liver, due to metastasis to that organ. Peripheral lymphadenopathy was found in 13 (41 per cent) of the patients and was generalized in 1 patient. Subcutaneous metastatic nodules were present in 5 cases (16 per cent). One patient presented clinical evidence of metastasis to the orbit. Neurologic signs due to involvement of the spinal cord were present in 1 case.

Primary Site. Although neuroblastomas may arise from sympathetic nervous tissue anywhere in the body, nearly half of all these tumors have their origin in the adrenal medulla. The most common sites of origin outside the adrenal are the retroperitoneal sympathetic ganglia in the abdomen, the pelvis and the thorax. In a few reported cases the primary site was in the

spinal column,[20,27] in the cervical sympathetic nerves,[45] and in 4 cases in adults reported by Ritter[42] the tumor had its origin in the small intestine. Isolated cases have been recorded in which the tumor arose in the celiac ganglion,[32] the organ of Zuckerkandl[15] and the ganglion nodosum of the vagus nerve.[36] One neuroblastoma arising in the subcutaneous tissues of the thigh has been reported in the literature.[24] In a number of reported cases, the lesion has originated in the eye or central nervous system. Most of these have probably been cases of retinoblastoma and medulloblastoma, which some authors have classified with the neuroblastomas.

In the adult, the primary tumor is usually extra adrenal.

The site of the primary tumor in our 32 cases is shown in Table I.

Of the 24 cases in which the tumor was primary in the abdomen, 13 (41 per cent of the total cases) were definitely adrenal in origin. The exact primary site could not be determined in the other 11.

Spread and Metastasis. The more undifferentiated neuroblastomas are locally invasive, and at the time of operation often will be found to have extended through the tumor capsule and to have involved adjacent structures so that complete surgical removal is impossible. Thus, in only 2 of our cases was complete surgical extirpation of the primary tumor accomplished. In both of these cases the tumor was of adrenal origin, was well encapsulated and could be removed without difficulty.

Neuroblastomas tend to metastasize early and widely, and in a considerable percentage of cases metastatic lesions will be present when the patient is first seen by a physician. Twenty-two (69 per cent) of the patients comprising this study presented evidence that metastasis had occurred at the time of admission. There appears to be no particular correlation between the size of the primary tumor and metastasis. Metastatic lesions may be widespread when the primary tumor is still small and clinically undetectable. In other instances the primary tumor may become large before metastasis occurs. Metastasis is chiefly by way of the blood stream but also may be by way of the lymph stream. In some cases of metastasis to the skull, spread may take place via the paravertebral veins.

TABLE I

SITE OF PRIMARY TUMOR IN 32 CASES OF NEUROBLASTOMA

	Number	Per cent
Abdomen	24	75
Chest	2	6
Spine	1	3
Unknown	5	16
Total	32	100

The patient with neuroblastoma usually runs a rapidly worsening course with involvement of the skeleton, lymph nodes, liver, meninges, skull and various other organs. In 1 of our patients coming to necropsy, almost every organ in the body, including the heart, was involved by metastatic lesions.

Much confusion has arisen with regard to the concept of the Pepper and Hutchison syndromes in neuroblastoma. In 1901 Pepper[38] reported some remarkable similarities in 6 cases (1 of his own). The initial symptoms of each patient appeared by the age of five weeks; each patient was dead by the age of sixteen weeks; each had extensive metastasis to the liver, and the primary tumor of each was in the right adrenal gland. The clinical picture was that of abdominal distention due to enlargement of the liver and abdominal lymph nodes. Hutchison's[23] paper, which appeared in 1907, described 10 cases of sarcoma of the suprarenal gland with metastasis to the orbit and the skull. In 4 of his patients the primary tumor was in the right adrenal gland and in 6 in the left adrenal gland. The striking clinical features were swelling about the skull, proptosis and discoloration of the eyelid.

Nothing indicates that either Pepper or

Hutchison intended to identify a syndrome, either clinical or anatomic. It was Frew,[17] in 1911, who introduced the concept of the Pepper and Hutchison syndromes. He ascribed the clinical picture of abdominal swelling and enlargement of the liver to metastasis from neuroblastomas of the right adrenal. This he called the "Pepper syndrome." The clinical picture of swelling about the skull and orbital and skeletal metastasis he believed due to primary tumors of the left adrenal, and he termed this the "Hutchison syndrome." Frew's theory has been repeatedly proved incorrect.[25,39,40] Neuroblastoma is the only neoplastic disease in which such a classification has been set up on the basis of the distribution of the metastatic lesions. In our group metastasis to the skull and skeleton had occurred oftener in cases in which the primary tumor was in the right adrenal than in those in which it was in the left adrenal gland. Metastasis to the liver, however, was somewhat more common in neuroblastomas of the right adrenal gland, probably due to contact made between the right adrenal gland and the so-called bare area of the liver. Our findings further indicate the lack of any significant relationship between the site of the primary tumor and the metastatic spread. Although the contributions of Pepper and Hutchison to the early literature on neuroblastoma were of considerable importance, the concept of the Pepper and Hutchison syndromes as described by Frew had best be laid to rest, once and for all.

Regression to Benign Ganglioneuroma. A striking feature of the natural history of neuroblastoma is the reported tendency of the tumor in some cases to regress spontaneously and to undergo transformation into benign ganglioneuroma. Several such cases have been reported in the literature and seem well-authenticated. In 1927 Cushing and Wolbach[12] reported the first case. Their patient at the age of two years had a dumbbell tumor in the midthoracic region causing paraplegia and intracranial metastasis with papilledema and cerebellar ataxia. Biopsy of the extraspinal portion of the tumor revealed neuroblastoma. The patient was treated with Coley's toxins, and the signs of intracranial tumor disappeared. Ten years later Cushing removed the residual intraspinal portion of the tumor; it was encapsulated and noninfiltrating and histologically was a ganglioneuroma.

Van Creveld and van Dam[11] have recorded the case of a girl, one and one-half years old, who had a large intra-abdominal neuroblastoma which could not be surgically removed. No treatment was given. When the patient was seen one and one-half years later, the tumor had diminished in size and four years later was completely gone.

Wittenborg[49] has observed 3 patients with localized tumor who were alive and well more than three years after biopsy alone.

Farber's[15] three observations concerning the natural history and response to treatment of neuroblastoma are as follows: 1. The tumor may undergo spontaneous hemorrhage and necrosis and disappear without treatment. 2. The tumor may undergo spontaneous maturation and become a benign ganglioneuroma. 3. The tumor may be treated successfully by a combination of surgical intervention and irradiation, even after metastasis to the liver has occurred.

It seems likely that benign transformation takes place in some cases of neuroblastoma after irradiation. A number of cases of proved metastatic lesions in the liver has been reported in which the patients have survived for several years in good health following irradiation of the primary tumor.[2,8,15,16,18,22,30,49,51] Our experience does not include any case in which the strange phenomenon of spontaneous regression or benign transformation has occurred.

Treatment. The treatment of choice in neuroblastoma is complete surgical extirpation of the tumor. As this is not often possible, a combination of surgical measures and irradiation will be necessary in

most cases if cure is to be hoped for. For a discussion of the treatment of neuroblastoma, the reader is referred to the classic paper of Wittenborg,[49] and that of Wyatt and Farber.[51]

Neuroblastomas are moderately radiosensitive. If they are attacked by complete surgical resection when this is possible, or by roentgen therapy, even after extension to the regional lymph nodes and liver, there is a reasonable chance of cure. In 5 patients in our series local invasion made complete surgical removal impossible, yet the patients have survived two, three and one-half, four, five and twelve years following irradiation and had no evidence of recurrence when last observed. When distant metastatic lesions are present, however, cure is not to be expected. None of our patients has survived more than a year after the discovery of a distant metastatic lesion.

FIG. 1. Intra-abdominal neuroblastoma, weight 650 gm. The well-formed capsule and marked lobulations are characteristic. Necrosis and degeneration are present and there are areas of calcification within the tumor.

PATHOLOGIC FEATURES

Gross Appearance. Neuroblastomas are often small tumors when first discovered but they may become large. The largest tumor in the present series which could be removed and examined measured 15 by 18 by 10 cm. and weighed 1,358 gm. One of the tumors seen earlier at this institution which was reported on by Poore[40] weighed 3,650 gm. and measured 25 by 18 by 20 cm.

The tumors, when small, were usually well encapsulated, but as they became larger they tended to break through the capsule and grow luxuriantly to involve adjacent structures, such as the kidney, aorta, inferior vena cava, or, in the case of intrathoracic tumors, the chest wall. In some instances it was impossible to determine the exact site of origin of the tumor.

Characteristically, the surface of the tumor was lobulated and a distinct well-formed fibrous capsule was present (Fig. 1). On the cut surface the flesh-colored tumor was friable, and lobulations were seen easily. Fine areas of calcification were sometimes visible on the cut surface.

Microscopic Aspects. Histologically, the architecture of the tumors varied considerably. In some cases most of the tumor was composed of dense masses of small dark cells which were similar to, but slightly larger than, lymphocytes. In other cases the tumor was relatively acellular, with occasional nests of cells lying among "brushy" masses of neurofibrils. Most tumors seemed to fall somewhere between these extremes, exhibiting each of these histologic patterns. In some tumors a large portion consisted of mature cellular structures resembling ganglion cells but with scattered islands of immature highly malignant cells. Because of this extreme variation from mature to immature cells within the same tumor, the Broders method of microscopic grading has not been generally applicable to neuroblastomas. We have chosen to designate the tumors showing a predominantly mature structure as ganglioneuroblastomas.

Architecturally two characteristics have been legendary in the microscopic description of neuroblastoma. The first is the arrangement of several cells into "rosettes," consisting of one or more layers of cell nuclei (Fig. 2). "Rosettes" were found in about 85 per cent of all our primary neuro-

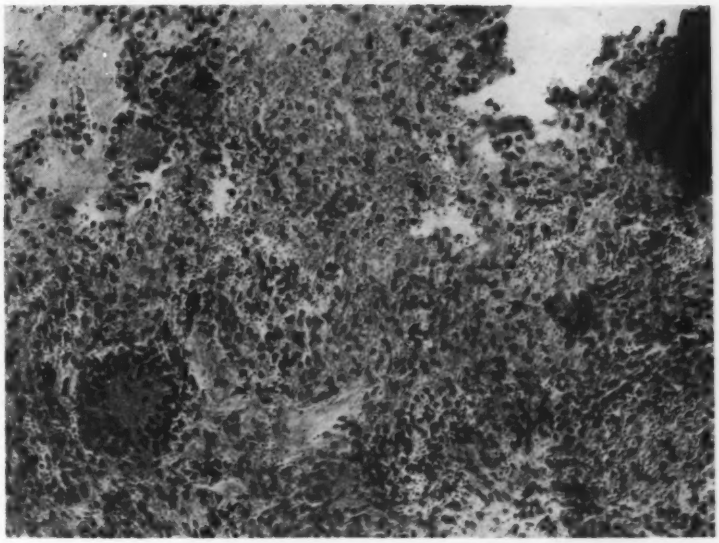


Fig. 2. Adrenal neuroblastoma showing rosette formation. The center of these is composed of neurofibrils. Area of calcification in the upper right (hematoxylin and eosin; ×95).

blastomas. They were seen less frequently in the metastatic lesions. The second characteristic is the presence of neurofibrils. These may be found anywhere in the tumor but are particularly likely to be found within the rosettes. Whenever these characteristic findings are absent, as they sometimes are, diagnosis may be difficult.

Areas of calcification were seen microscopically in about half of our primary tumors, most frequently in the more mature type of tumors. Calcification in the metastatic lesions was rare. Invasion of veins was occasionally seen.

The importance of adequate histologic examination in every case, with examination of multiple sections from various portions of the tumor, cannot be overemphasized.

ROENTGENOLOGIC FINDINGS

The roentgenologic signs of neuroblastoma may be produced by the primary tumor, the metastatic lesions, or by both, and may be varied depending on the site of involvement.

Abdomen. Roentgenograms of the abdomen were obtained in 22 of the 24 cases in which the tumor was primary in the abdomen. In 18 there was roentgenologic evidence of an abdominal mass. The commonest finding was a rounded mass of water density with ill-defined borders. In cases in which the tumor was large, the mass often could be seen to extend across the midline of the abdomen. In 2 cases the abdominal roentgenogram indicated anterior and upward displacement of the transverse colon, apparently by a large retroperitoneal mass. In several cases, calcification could be seen, but no definite mass could be visualized.

Metastasis within the abdomen often produces enlargement of the liver or regional lymph nodes. In 3 cases enlargement of the liver due to metastatic involvement of this organ was visible. In 1 case a fusiform soft tissue mass, due apparently to enlarged para-aortic lymph nodes, could be seen extending on each side of the lower thoracic and upper lumbar vertebrae.

The importance of the presence of calcification in the tumor in the diagnosis of neuroblastoma has been pointed out by several authors.[33,37,43,44,51] Calcification was present in 7 (32 per cent) of our 22 cases of primary abdominal neuroblastoma in which roentgenograms of the abdomen were available for study. This usually appeared as finely stippled areas of calcium deposits scattered irregularly throughout a large portion of the tumor (Fig. 3) and in a few cases some areas of confluent, homogeneous calcification. In 1 case the tumor was

FIG. 3. Adrenal neuroblastoma with calcification.

densely and homogeneously calcified throughout, while in another the area of calcification was only a few millimeters in diameter and was barely visible in the plain roentgenogram of the abdomen. Roentgenologically detectable calcification was not found in the metastatic lesions of neuroblastoma in any case.

Excretory Urography. Nineteen of the 24 patients with primary abdominal neuroblastoma had excretory urograms made, and findings were abnormal in 15 (79 per cent). The commonest urographic abnormality, displacement of a kidney, was evident in 12 cases (Fig. 4*a*). This varied from slight downward displacement to marked downward and lateral displacement of the kidney. There was no evidence of invasion of the kidney or renal calyces, but a varying degree of distortion of the calyceal system, due to extrinsic pressure from the tumor, was present in almost every case of renal displacement. In 3 cases a definite mass was seen at the upper pole of a kidney in the adrenal area without displacement of the kidney or other urographic abnormality.

Displacement of a ureter from its normal course was found in 2 cases. In 1, both ure-

FIG. 4. (*a*) Excretory urogram showing displacement of left kidney in a case of adrenal neuroblastoma. (*b*) Neuroblastoma arising from the lumbar sympathetic nerves. Tumor shows calcification and extends across the midline. Both ureters are displaced laterally, and there is hydronephrosis on the left.

ters were displaced laterally by a huge tumor which probably arose from the lumbar sympathetic nerves (Fig. 4*b*) and extended well across the midline. Mild unilateral hydronephrosis was present secondary to compression of one ureter. This is the only patient we have seen with any evidence of urinary obstruction, although several such cases have been reported by other observers.[3,21]

Thorax. Neuroblastoma primary in the thorax arises from the paravertebral sympathetic nerves and usually appears in the roentgenogram as a rounded, often sharply circumscribed mass adjacent to the posterior mediastinum. Ribs may be eroded or displaced, and the tumor may extend to involve the spinal column. The esophagus or trachea may be displaced in some cases. Calcification is sometimes evident within the tumor, but this is less frequent than in primary abdominal neuroblastoma.

The tumor was primary in the thorax in 2 of the 32 cases studied. In both instances it appeared in the roentgenogram as a rounded, well-circumscribed mass in the right paravertebral region, protruding into the apex of the right lung. No calcification was present in either of these cases. The larger of these 2 tumors occurred in an eleven year old boy and measured 10 cm. in diameter (Fig. 5). Adjacent bony or mediastinal structures were not involved. The other patient was a one month old boy, the youngest patient in the entire group. The initial symptoms in this case, dyspnea and cyanosis, were noted when the child was three weeks of age. The esophagus and trachea were displaced roentgenologically. The right second rib was displaced laterally and rotated posteriorly by the tumor, and the posterior portion of the rib was eroded (Fig. 6). The roentgenologic findings in these 2 cases would not serve to differentiate neuroblastoma from an intrathoracic neurofibroma or ganglioneuroma. In both of these patients the tumor had involved the pleura, and only about 95 per cent of the tumor could be removed at operation. Irradiation was given postoperatively. One patient has survived twenty-one months and the other four years without evidence of recurrence.

Neuroblastoma occasionally metastasizes to the mediastinal lymph nodes, but pulmonary metastasis is relatively uncommon and tends to occur late in the course of the disease. Two of the 32 patients had

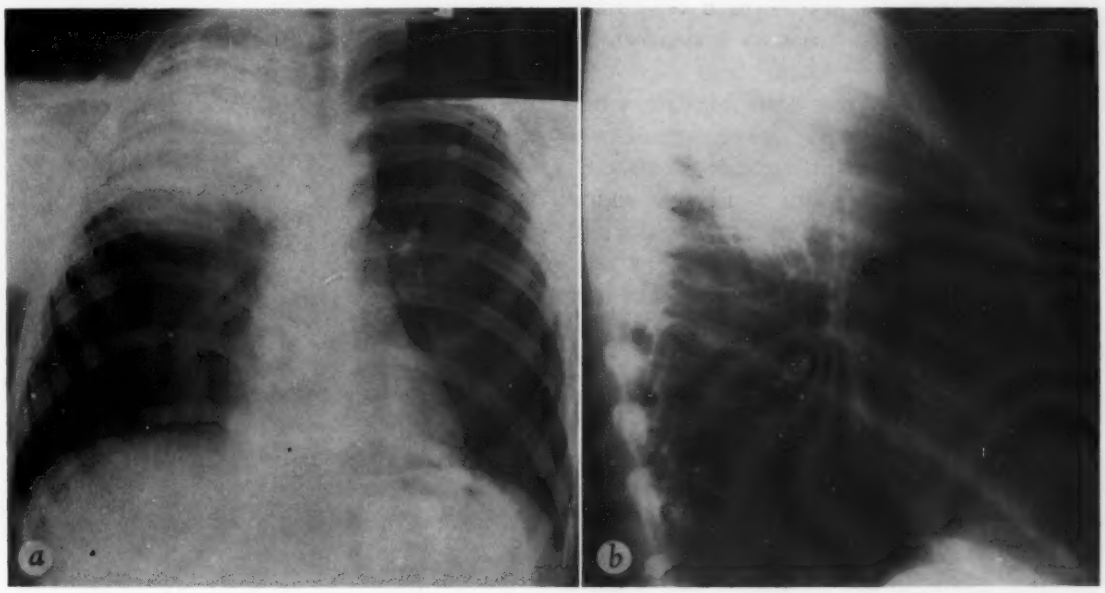


Fig. 5. (*a* and *b*) Large intrathoracic neuroblastoma.

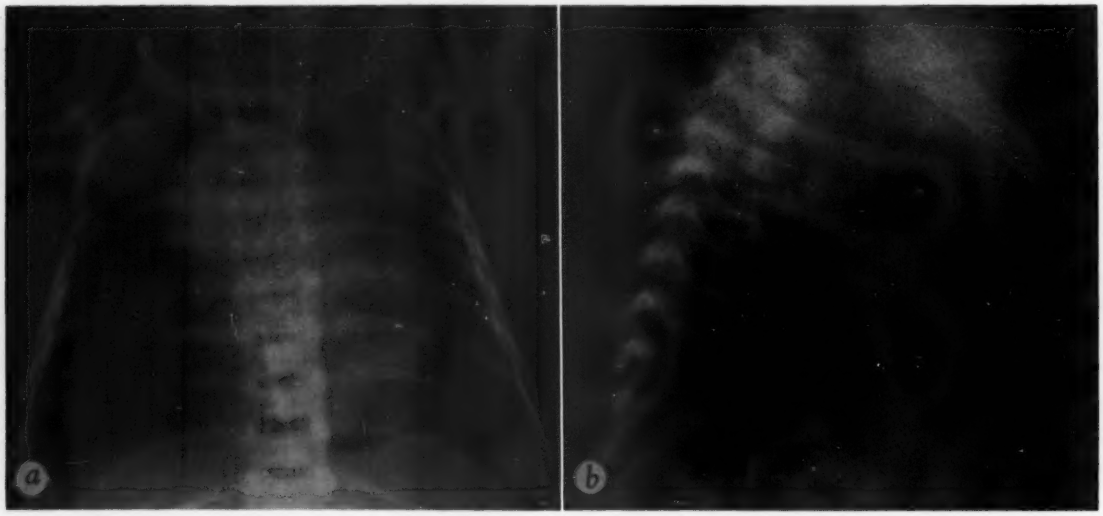


FIG. 6. (*a* and *b*) Intrathoracic neuroblastoma in a one month old infant. The right third rib is eroded and rotated dorsally by the tumor.

enlarged hilar and mediastinal lymph nodes, due to metastasis. Pulmonary metastasis had occurred in only 1 patient, and in this case only a single pulmonary lesion was present. Several cases of multiple or widespread pulmonary metastatic lesions have been reported in the literature. The infrequent occurrence of pulmonary metastasis, even in the presence of widespread involvement of the skeleton and other organs, is a noteworthy feature of neuroblastoma and may serve as a differential diagnostic aid.

Skeleton. Metastatic neuroblastoma has a special predilection for the skeleton. Survey roentgenograms of the long bones, spinal column, pelvis and skull were made in most of our cases when the diagnosis of neuroblastoma was suspected or made. Fourteen (44 per cent) of the patients had skeletal metastasis. Involvement of multiple bones was present in every case except 1. In no case was a metastatic lesion found distal to the wrist or ankle. The relative frequency of involvement of individual bones is shown in Table II. Although lesions in the long bones tended to occur in the ends of the bones near the epiphyses, other portions of the shafts were involved in some cases, and occasionally the entire length of the shaft was involved. The epiphysis was involved in only 1 case.

A striking feature of the skeletal lesions was their tendency toward a bilaterally symmetrical distribution (Fig. 7*a*). In 9 of the 14 patients with skeletal lesions, the lesions were bilaterally symmetrical, not only as to bilateral involvement of the same bones but also as to location within the bones; for instance, the medial aspect of the lowermost portion of both femora. This unusual feature was noted even in cases in which skeletal involvement was not widespread.

TABLE II

INVOLVEMENT OF INDIVIDUAL BONES IN 14 CASES OF NEUROBLASTOMA WITH SKELETAL METASTASIS

Skull and jaws	10
Humerus	8
Femur	7
Pelvis	5
Tibia	4
Scapula	4
Ribs	3
Fibula	2
Radius	2
Ulna	2
Spine	1
Clavicle	1

Fig. 7. (*a*) Bilaterally symmetrical involvement of the femora and tibiae. Changes are purely destructive. (*b*) Same case as *a*. Bone lesions in any one patient were nearly always of the same type. In no instance was a purely destructive lesion in one bone associated with a predominantly productive lesion in another bone.

Generally, all the skeletal lesions in each patient were of the same type. In no instance was a purely destructive lesion in one bone associated with a predominantly productive lesion in another bone (Fig. 7*b*). It was thus possible to group the cases according to the general type of bone change present. In most cases the lesions in bones showed roentgenographic evidence of both destruction and production of bone, an observation of considerable importance in the differentiation of metastatic neuroblastoma from certain other lesions in the skeleton. In 77 per cent of the cases in which the long bones were involved, the lesions were of the mixed destructive and productive types (Fig. 8*a*). In only 23 per cent were the lesions purely destructive. In no instance was proliferation of bone noted without evidence of destructive change also. In the flat bones of the pelvis, the scapulae, and ribs the predominance of mixed destructive and productive changes was even more striking and the productive changes seemed proportionately greater than in the long bones (Fig. 9). In 6 (67 per cent) of the 9 cases in which metastatic lesions were found in the bones of the skull, the lesions were of the destructive and proliferative type, whereas in 3 cases (33 per cent) the lesions were purely destructive.

Another important feature of the skeletal lesions is the frequency of cortical destruction. This is most commonly seen in the long bones. In 7 (78 per cent) of the 9 cases in which the long bones were involved, some degree of destruction of the cortex was evident. In some cases the metastatic process may extend the full length of the shaft before cortical destruction occurs. In some of these cases, bone production will not be evident and the appearance at this stage is not unlike that of diffuse osteoporosis. Cortical destruction is uncommon in the flat bones of the pelvis and scapulae. In only one instance was cortical destruction found in these bones, this instance being in the scapula. When cortical destruction is present, the tumor mass may be seen in some instances to extend into the

FIG. 8. (*a*) Diffuse involvement of the shaft showing mixed destructive and productive changes and parallel type of periosteal reaction. Pathologic fracture in the upper humerus. The scapula is also involved. (*b*) Periosteal reaction of the parallel type in the lower part of the femur. The perpendicular or "sunburst" type of periosteal reaction seen here in the fibula is rarely encountered in the long bones.

adjacent soft tissues. This occurred in 1 case in which there was extensive metastatic destruction of a portion of the clavicle.

Periosteal reaction is a common finding in neuroblastoma, particularly in the long bones and skull. In 60 per cent of the cases in which the long bones were involved periosteal reaction was observed. This was of the parallel type in all the cases except 1. In this one exception the perpendicular or "sunburst" type of periosteal reaction was associated with a metastatic lesion of the fibula (Fig. 8*b*). The other bones involved in this same case showed the usual parallel type of periosteal reaction. Occasionally, the periosteal reaction extended almost the entire length of the shaft of a long bone, and this was sometimes present when the underlying bone was still fairly normal in appearance or showed early diffuse involvement without definite destructive or productive changes. In these cases the roentgenologic appearance of the bone will be similar to that seen in leukemia, and the case will often be misdiagnosed as such. Periosteal reaction was not found in the flat bones of the pelvis and scapula in any of the cases. In 1 of the 3 cases with rib involvement periosteal reaction of the parallel type was present.

Pathologic fractures sometimes occur in the long bones and in the spine. Such fractures were present in 2 patients, 1 having

a pathologic fracture in the surgical neck of the humerus and 1 a pathologic fracture in a thoracic vertebra.

The appearance of metastatic neuroblastoma in the skull often is characteristic. Although occasionally only one or more rather discrete osteolytic lesions develop in the skull, usually large areas are involved and the margins of the lesions are irregular and indistinct. In the skull, as in the other bones, there is usually evidence of proliferation of bone, as well as destruction. In 6 of the 9 cases the metastatic lesions in the skull were of this mixed type, while in 3 cases the lesions were purely destructive. In 1 case, only the mandible was involved and the tumor mass had caused extrusion of a tooth from the mandible.

Metastasis to the meninges and brain with evidence of increased intracranial pressure is often associated with metastasis to the skull. Roentgenologic signs of increased intracranial pressure with separation of the sutures were noted in 4 of the 9 cases of metastasis to the skull. In 2 of these the perpendicular or "sunburst" type of periosteal reaction was present, with perpendicular spicules of new bone extending into the soft tissues of the scalp. When this type of periosteal reaction is accompanied by separation of the sutures due to increased intracranial pressure and by osteolytic and osteoblastic lesions in the skull, the diagnosis of metastatic neuroblastoma can be made with great certainty (Fig. 10*a*). No other condition in our experience produces this picture. The parallel type of periosteal reaction was not present in the skull in any of the cases.

Metastasis to the orbit has been reported by some observers as being a common fea-

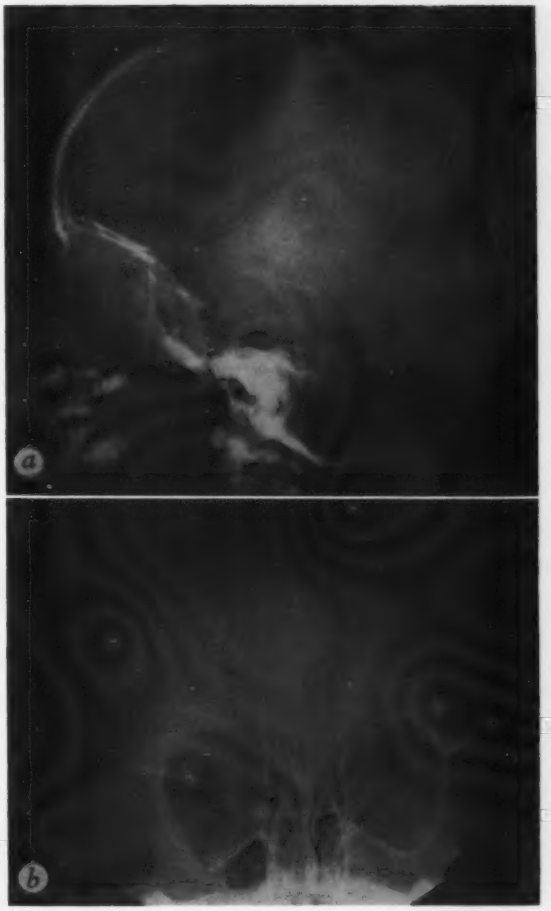


Fig. 10. (*a*) Well-developed characteristic changes of neuroblastoma in the skull. (*b*) Metastasis to orbit in another case with increased soft-tissue density in the orbit. Destruction and reactive bony sclerosis are present in the roof of the orbit.

Fig. 9. Mixed osteolytic and osteoblastic metastatic lesions in pelvis and femora.

ture of neuroblastoma.[5,7,9,26,44,51] Only 1 of the 32 patients in our group had clinical or other evidence of such metastasis. In this case the posteroanterior roentgenogram of the skull and special views of the orbit showed increased soft tissue density in the orbit with destruction of the superior rim of the bony orbit and reactive sclerosis around this area (Fig. 10*b*). Orbital metastasis is considered the result of direct extension from metastatic lesions in the skull and meninges.

The important roentgenologic features of the skeletal lesions in the 32 cases of neuroblastoma studied were (1) marked tendency to a bilaterally symmetrical distribution of the lesions, even when metastasis in the skeleton is not widespread; (2) the predominance of mixed destructive and proliferative changes in bone; (3) the frequent finding of cortical destruction and periosteal reaction; (4) the occasional finding of a pathologic fracture, and (5) the distinctive changes in the skull.

DIFFERENTIAL DIAGNOSIS

Roentgenologically, the conditions most likely to be confused with neuroblastoma are Wilms' tumor, lymphoblastoma, leukemia, Ewing's tumor, reticuloendotheliosis, osteomyelitis, and, in the thorax, benign neurogenic tumors. The skill of the roentgenologist in distinguishing these conditions depends not only on his familiarity with their roentgenologic characteristics but also on his knowledge of the pathology and natural history of these diseases.

It is highly important that adequate roentgenologic examination be carried out in every case. Whenever neuroblastoma is suspected or when an abdominal mass or skeletal lesion which is suggestive of a neuroblastoma has been found, the patient should have roentgenologic examination of all possible areas of involvement. Roentgenograms of the abdomen, thorax, spinal column, skull and long bones should constitute the minimal examination. Excretory urograms are sometimes helpful when there is an abdominal mass. Any other special examination should be carried out as indicated.

Since neuroblastoma frequently presents as an abdominal mass, the problem of differentiation from Wilms' tumor arises. Both Wilms' tumor and neuroblastoma occur in the same age group and in the same general region of the abdomen. The roentgenologic appearance of the primary abdominal tumor in both conditions is seldom such that a specific diagnosis can be made. Differentiation in the absence of metastasis is often impossible, but several points may be helpful. Calcification within the tumor, when present, is one of the most important differential signs. Calcification within the tumor is seen in a third of all cases of abdominal neuroblastoma but is extremely rare in Wilms' tumor. Occasionally, in the excretory urogram, an adrenal neuroblastoma will be seen to be extrinsic to the kidney. Calyceal deformity is not a reliable differential sign. Neuroblastomas often extend across the midline of the abdomen when large, a feature which is said to occur rarely in cases of Wilms' tumor. Skeletal metastasis is not as common in Wilms' tumor as in neuroblastoma and tends to occur late in the course of the disease. The bone lesions in Wilms' tumor are almost always purely osteolytic; cortical destruction and periosteal reaction are rarely seen. There is no tendency toward a bilaterally symmetrical distribution of the skeletal lesions in Wilms' tumor as is often the case in neuroblastoma. Pulmonary metastasis is common in Wilms' tumor and occurs early, whereas in neuroblastoma pulmonary lesions are relatively rare and tend to occur late and after skeletal lesions have developed. The pathognomonic appearance of the skull lesions in neuroblastoma, when present, serves to differentiate the two conditions.

Lymphoblastoma tends to occur in a somewhat older group than neuroblastoma; it rarely is seen in young children and almost never in infants. An abdominal mass due to lymphoblastoma will not show evidence of calcification. Skeletal lesions are

not common in lymphoblastoma and do not have the symmetrical distribution so often seen in neuroblastoma. There is usually little or no evidence of bone production and cortical destruction, and periosteal reaction does not often occur.

Neuroblastoma involving the skeleton is probably more often confused roentgenologically with leukemia than with any other condition. In the occasional case of neuroblastoma in which the full length of the shaft of a long bone is involved without cortical destruction, and with or without the parallel type of periosteal reaction, differentiation from leukemia may be difficult. In most cases, however, these two conditions can be differentiated on the basis of the skeletal changes. The generalized skeletal demineralization seen in leukemia is not often found in neuroblastoma. In neuroblastoma the changes will be confined to those bones involved by metastatic lesions; the remainder of the skeleton will appear normal. In leukemia the bone changes are usually purely destructive in contrast to the mixed destructive and productive changes seen in the majority of cases of neuroblastoma. The transverse bands of radiolucency which are seen in leukemia just beneath the epiphyses of the long bones are never seen in neuroblastoma. Although the periosteal reaction in the two conditions may be similar, cortical destruction usually is absent in leukemia whereas it was present in 77 per cent of our cases of neuroblastoma. In leukemia the process does not extend into the soft tissues adjacent to the bone. Pathologic fractures, the skull changes characteristic of neuroblastoma and calcified abdominal tumors are not seen in leukemia.

The similar appearance of skeletal neuroblastoma and Ewing's tumor has been noted by several authors.[1,10,35,48] Ewing's tumor may spread to involve multiple bones and the cortical destruction and periosteal reaction may be much like that seen in neuroblastoma. In most instances, however, differentiation will not be difficult. Ewing's tumor usually presents as a solitary bone lesion, most often seen in the midshaft. Neuroblastoma rarely occurs as a solitary bone lesion and when it does the lesion will be very small, as it will have little opportunity to grow before other metastatic lesions appear in bone. In addition, there may be evidence of neuroblastoma elsewhere, such as in the abdomen or skull. Ewing's tumor is uncommon in children less than ten years of age and is rare in a child less than five years of age, when the incidence of neuroblastoma is greatest. Differentiation of other primary bone tumors, such as osteogenic sarcoma and reticulum cell sarcoma, from neuroblastoma usually presents no problem.

The reactive proliferation of bone and periosteal reaction seen in osteomyelitis may simulate the changes of neuroblastoma. The symmetrical involvement of multiple bones in metastatic neuroblastoma will usually serve to differentiate the two conditions.

Reticuloendotheliosis is sometimes confused roentgenologically with neuroblastoma, but there is actually little similarity in the appearance of these two diseases. The sharply punched out lesions of reticuloendotheliosis in the skull and other bones are not seen in neuroblastoma. The lesions of reticuloendotheliosis are purely destructive, although in rare instances periosteal reaction may be seen in the long bones.

The presence of an abdominal mass or the skull changes of neuroblastoma are of obvious importance in distinguishing neuroblastoma from these various conditions involving the skeleton.

Primary intrathoracic neuroblastomas arise in the same location and produce the same roentgenologic appearance as other neurogenic tumors in the thorax. There are no roentgenologic criteria for distinguishing primary intrathoracic neuroblastomas, in the absence of metastasis, from neurofibromas and ganglioneuromas. These benign neurogenic tumors are slightly more common than neuroblastomas. They tend to occur in a somewhat older age group but may occur in children.

SUMMARY AND CONCLUSIONS

The clinical records and pathologic material were reviewed on 32 histologically proved cases of neuroblastoma seen at the Mayo Clinic in the ten year period through 1954. The roentgenograms of these patients were carefully studied in an attempt to establish the criteria for the roentgenologic diagnosis of this disease.

Although the appearance of the primary tumor is not characteristic, the presence of an abdominal mass or a mass in the thoracic paravertebral region in a child should always suggest the diagnosis of neuroblastoma. An abdominal mass which contains calcium, particularly if the mass is in the adrenal region, will in all probability be a neuroblastoma. Calcification in the region of the mass was visible in the roentgenogram in 32 per cent of the cases studied in which the tumor was primary in the abdomen. Such calcification is rare in Wilms' tumor and other conditions. Calcification is less commonly seen in primary intrathoracic neuroblastomas. Neuroblastomas arising in the thorax cannot be distinguished roentgenologically from other neurogenic tumors, any of which may show calcification.

Metastasis had occurred at the time of admission in 69 per cent of the patients. Forty-four per cent of the total group had skeletal metastasis. The site of the primary tumor and the distribution of metastatic lesions were not related; this observation further disproves the concept of the so-called Pepper and Hutchison syndromes.

The skeletal lesions of neuroblastoma are often distinctive, and the experienced roentgenologist frequently can make the diagnosis from the appearance of the bone changes alone. The important roentgenologic features of the skeletal lesions are: (1) a marked tendency to a bilaterally symmetrical distribution of the lesions; (2) a predominance of mixed destructive and proliferative bone changes; (3) the frequent finding of cortical destruction and periosteal reaction; (4) the occasional extension of the tumor process into the adjacent soft tissues, and (5) the occasional presence of pathologic fractures.

The evidence in the roentgenogram of mixed osteolytic and osteoblastic metastatic lesions in the skull, separation of sutures due to increased intracranial pressure, and the sunburst type of periosteal reaction is considered pathognomonic of neuroblastoma.

The importance of adequate roentgenologic examination in all cases of suspected neuroblastoma has been emphasized and certain minimal studies have been suggested.

Certain roentgenologic findings or combinations of findings are specific for neuroblastoma and in many instances the diagnosis can be made by the roentgenologist with a high degree of accuracy.

The Mayo Clinic
Rochester, Minnesota

REFERENCES

1. BARDEN, R. P. The similarity of clinical and roentgen findings in children with Ewing's sarcoma (endothelial myeloma) and sympathetic neuroblastoma. AM. J. ROENTGENOL. & RAD. THERAPY, 1943, *50*, 575–581.
2. BECK, S. M., JR., and HOWARD, P. J. Neuroblastoma; review of the literature and report of a six-year cure by roentgen therapy. *A.M.A. J. Dis. Child.*, 1951, *82*, 325–334.
3. BENEVENTI, F. A., and TWINEM, F. P. Neuroblastoma. *J. Urol.*, 1948, *60*, 235–241.
4. BERGSTROM, V. W. Congenital neuroblastoma of the adrenal. (Sympathoblastoma, sympathogonioma, ganglioma embryonale sympatheticum or sympathoma embryonale.) *Am. J. Clin. Path.*, 1937, *7*, 516–523.
5. BOTHMAN, L., and BLANKSTEIN, S. S. The eye in adrenal sympathicoblastoma (neuroblastoma); importance of ocular findings with first pathologic report of metasatic tumor in choroid. *Arch. Ophth.*, 1942, *n.s. 27*, 746–761.
6. BRODY, H. Congenital malignant neuroblastoma of the suprarenal gland in one of twin girls. *Am. J. Human Genet.*, 1950, *2*, 371–374.
7. BURCH, F. E. Orbital metastases from malignant tumors of the suprarenal gland. *Arch. Ophth.*, 1932, *n.s. 7*, 418–433.
8. Case Records of the Massachusetts General Hospital: Case 27392. Presentation of case. *New England J. Med.*, 1941, *225*, 510–513.

9. Clark, W. C. Adrenal neuroblastoma with particular reference to metastasis to the orbit; report of a case and notes on two other cases. *Arch. Ophth.*, 1939, *22*, 575–580.
10. Colville, H. C., and Willis, R. A. Neuroblastoma metastases in bones, with a criticism of Ewing's endothelioma. *Am. J. Path.*, 1930, *9*, 421–429.
11. van Creveld, S., and van Dam R. Prognosis of sympathoblastoma. (Abstr.) *Quart. Rev. Pediat.*, 1948, *3*, 313.
12. Cushing, H., and Wolbach, S. B. The transformation of a malignant paravertebral sympathicoblastoma into a benign ganglioneuroma. *Am. J. Path.*, 1927, *3*, 203–216.
13. Dodge, H. J., and Benner, Miriam C. Neuroblastoma of the adrenal medulla in siblings; a case report. *Rocky Mountain M. J.*, 1945, *42*, 35–38.
14. Dunn, J. S. Neuroblastoma and ganglioneuroma of the suprarenal body. *J. Path. & Bact.*, 1915, *19*, 456–472.
15. Farber, S. Neuroblastoma. *Am. J. Dis. Child.*, 1940, *60*, 749–751.
16. Forster, W. Neuroblastoma with recovery, *M. J. Australia*, 1944, *2*, 196.
17. Frew, R. S. On carcinoma originating in the suprarenal medulla in children. *Quart. J. Med.*, 1911, *4*, 123–140.
18. Goldring, D. Neuroblastoma sympatheticum with metastases; report of a case with apparent recovery. *J. Pediat.*, 1951, *38*, 231–234.
19. Hagstrom, H. T. Fetal dystocia due to metastatic neuroblastoma of the liver. *Am. J. Obst. & Gynec.*, 1930, *19*, 673–676.
20. Hamilton, P. K. Neuroblastoma of the spinal cord; report of a case. *Am. J. Clin. Path.*, 1951, *21*, 846–851.
21. Hepler, A. B. Presacral sympathicoblastoma in an infant causing urinary obstruction. *J. Urol.*, 1943, *49*, 777–784.
22. Hudson, H. W., Jr., Chamberlain, J. W., and Becker, F. B. Successful treatment of neuroblastoma; report of two cases with apparent cures. *New England J. Med.*, 1952, *246*, 536–537.
23. Hutchison, R. On suprarenal sarcoma in children with metastases in the skull. *Quart. J. Med.*, 1907, *1*, 33–38.
24. Jacobsen, V. C., and Hosoi, K. Primary sympathicoblastoma of the skin of the thigh. *Am. J. Path.*, 1930, *6*, 427–434.
25. Karsner, H. T. Distribution of metastases of neuroblastoma of the adrenal. *Tr. A. Am. Physicians*. 1942, *57*, 209–211.
26. Kuhn, H. S. Adrenal neuroblastoma and its ocular symptoms; a case report with autopsy. *Am. J. Ophth.*, 1939, *22*, 642–648.
27. Lampe, I. Neuroblastoma (?) in a dorsal vertebra. *Cancer Seminar*, 1951, *1*, 49–51.
28. Larimer, R. C. Neuroblastoma (sympathogonioma) of the adrenal in a newborn infant. *J. Pediat.*, 1949, *34*, 365–366.
29. Lehman, E. P. Neuroblastoma; with report of a case. *J. M. Research*, 1917, *36*, 309–325.
30. Lehman, E. P. Adrenal neuroblastoma in infancy; fifteen year survival. *Ann. Surg.*, 1932, *95*, 473.
31. Lewis, D., and Geschickter, C. F. Tumors of the sympathetic nervous system; neuroblastoma, paraganglioma, ganglioneuroma. *Arch. Surg.*, 1934, *28*, 16–58.
32. Lucas, P. J. Neuroblastoma with origin in the celiac ganglion. *M. Times, New York*, 1940, *68*, 411–417; 434.
33. Mandeville, F. B. Calcification in sympathoblastoma (neuroblastoma). *Radiology*, 1949, *53*, 403–405.
34. Marchand, F. Beiträge zur Kenntniss der normalen und pathologischen Anatomie der Glandula carotica und der Nebennieren. In: Internationale Beiträge zur wissenschaftlichen Medizin, vol. 1, Anatomie, Physiologie und Entwicklungsstörungen. August Hirschwald, Berlin, 1891, pp. 535–581.
35. Neely, J. M., and Rogers, F. T.: Roentgenological and pathological considerations of Ewing's tumor of bone. Am. J. Roentgenol. & Rad. Therapy, 1940, *43*, 204–210.
36. Pack, G. T., Ariel, I. M., and Miller, T. R. Malignant ganglioneuroma of the ganglion nodosum of the vagus nerve. *A.M.A. Arch. Surg.*, 1953, *67*, 645–660.
37. Parsons, P. B., and Platt, L. Calcification in abdominal neuroblastoma; report of two cases. Am. J. Roentgenol. & Rad. Therapy, 1940, *44*, 175–177.
38. Pepper, W. A study of congenital sarcoma of the liver and suprarenal; with report of a case. *Am. J. M. Sc.*, 1901, *121*, 287–299.
39. Phillips, R. Neuroblastoma. *Ann. Roy. Coll. Surgeons England*, 1953, *12*, 29–48.
40. Poore, T. N. Abdominal neuroblastomas. Thesis, Graduate School, University of Minnesota, 1949.
41. Potter, Edith L., and Parrish, J. M. Neuroblastoma, ganglioneuroma and fibroneuroma in stillborn fetus. *Am. J. Path.*, 1942, *18*, 141–148.
42. Ritter, S. A. Neuroblastoma of the small intestine. *Am. J. Surg.*, 1938, *n.s. 41*, 486–493.
43. Samuel, E. Calcification in suprarenal neoplasms. *Brit. J. Radiol.*, 1948, *n.s. 21*, 139–142.
44. Sherman, R. S., and Leaming, R. The roentgen findings in neuroblastoma. *Radiology*, 1953, *60*, 837–849.
45. Stewart, M. J. Neuro-blastoma of the cervical sympathetics. *J. Path. & Bact.*, 1919, *23*, 119–120.

46. VIRCHOW, R. Die krankhaften Geschwülste. Vol. 2, August Hirschwald, Berlin, 1864–1865, 756 pp.

47. WELLS, H. G. Occurrence and significance of congenital malignant neoplasms. *Arch. Path.*, 1940, *30*, 535–601.

48. WILLIS, R. A. Metastatic neuroblastoma in bone presenting the Ewing syndrome; with discussion of "Ewing's sarcoma." *Am. J. Path.*, 1940, *16*, 317–331.

49. WITTENBORG, M. H. Roentgen therapy in neuroblastoma; review of seventy-three cases. *Radiology*, 1950, *54*, 679–687.

50. WRIGHT, J. H. Neurocytoma or neuroblastoma, a kind of tumor not generally recognized. *J. Exper. Med.*, 1910, *12*, 556–560.

51. WYATT, G. M., and FARBER, S. Neuroblastoma sympatheticum; roentgenological appearances and radiation treatment. AM. J. ROENTGENOL. & RAD. THERAPY, 1941, *46*, 485–495.

METASTATIC RETINOBLASTOMA AS A CAUSE OF DIFFUSE INTRACRANIAL CALCIFICATION*

By LAWRENCE A. DAVIS, M.D., *and* ISRAEL DIAMOND, M.D.
LOUISVILLE, KENTUCKY

EXTENSIVE calcification within the brain substance is rare. The most frequent cause in the first six months of life is probably toxoplasmosis, but the possibility of other infections (including cytomegalic inclusion disease[2]), anomalies, and neoplastic disease must be kept in mind.[1]

Calcification in retinoblastoma has been identified in as high as 75 per cent of cases,[5] and has been limited to the orbit in all reported cases to our knowledge. Calcification can frequently be detected before surgery, but in many cases it only becomes evident after roentgenographic examination of the operative specimen.[3–7]

This report concerns extensive intracerebral calcifications associated with hydrocephalus in an infant with uniocular retinoblastoma extending into the middle cerebral fossa and producing extensive visceral metastases. Roentgenographically, the calcifications were punctate and appeared to be in, or adjacent to, the basal ganglia on the left side. There was marked hydrocephalus with distortion of the ventricular system (Fig. 1 and 2).

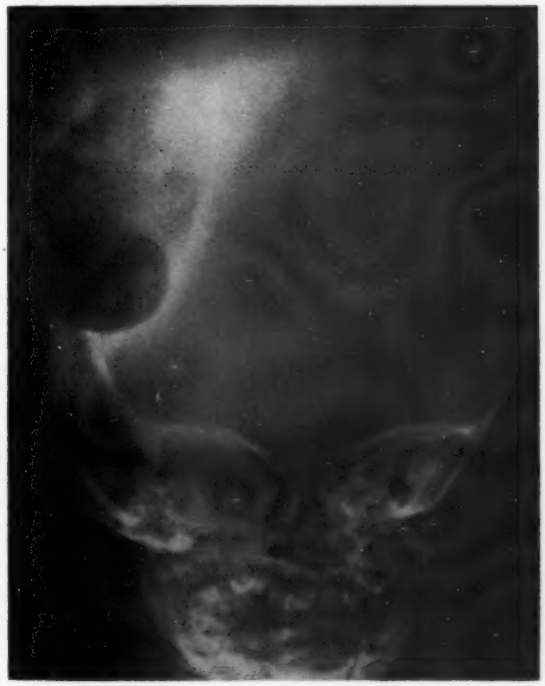


FIG. 1. Roentgenogram of the skull demonstrating diffuse calcification in left frontoparietal area. The ventricles are markedly dilated.

FIG. 2. Same as Figure 1, lateral view.

REPORT OF A CASE

A four month old colored female infant was admitted to the Children's Hospital because of a rapidly enlarging head and abnormal ocular

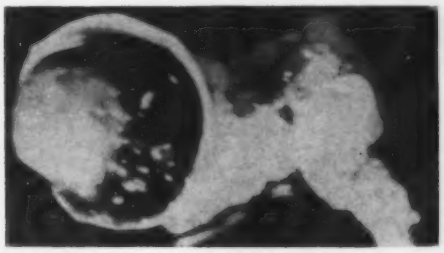


FIG. 3. Right eye bisected coronally to show the primary tumor. Note the thickening of the nerve due to tumor replacement.

* From the Departments of Radiology and Pathology, The Children's Hospital and the University of Louisville Medical School, Louisville, Kentucky.

FIG. 4. Tumor mass at base of brain filling the interpeduncular fossa and invading the basal ganglia.

movements. The child weighed only 8 pounds, 12 ounces, and was markedly dehydrated. The head measured 43 cm. in circumference and the thorax 34 cm. All the sutures were separated 1 cm. The anterior fontanelle measured 8 by 9 cm. and was tense and bulging. The scalp veins were distended. The patient was apparently blind. There were definite abnormalities in the right fundus with elevation of the retina due to a yellowish-white retroretinal mass. The right eye gave a yellow reflex of the "cat-eye." The heart and lungs were normal. The liver was palpable 1 cm. below the costal margin. The child died three weeks later following an uneventful hospital course.

Postmortem examination revealed a primary retinoblastoma arising in the right eye. The tumor presented as an ovoid gelatinous disk, 1.5 cm. in diameter and 1 cm. in thickness, attached to and covering the posterior aspect of the choroid. No retina was apparent. The mass was semitranslucent, yellow, and studded with numerous white specks of calcification (Fig. 3). The tumor extended posteriorly, destroying the optic nerve and expanding the optic foramen to a diameter of 1 cm. In the

FIG. 5. Subarachnoid seedings of tumor showing foci of calcification. Left temporal lobe.

FIG. 6. Liver, inferior and cut surface, showing metastasis.

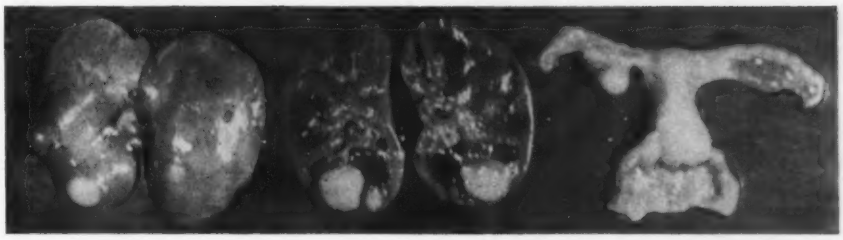


Fig. 7. Kidneys and left ovary showing metastases.

subarachnoid space it formed a mass measuring 2.5 by 6.5 cm., occupying the interpeduncular fossa and invading the overlying brain (Fig. 4). The pituitary gland was completely replaced by tumor. The mass displaced the temporal lobes laterally, but did not invade them directly. The optic chiasm, the proximal halves of the olfactory nerves, and nerves III, IV, V, and VI were invaded and obscured by the tumor. On section of the mass a distinct grittiness was encountered. Tumor seeding, characterized by a small amount of yellow, clear gelatinous material speckled with yellow to white opaque particles, was found over the inferior surface of the left temporal lobe (Fig. 5).

There was marked internal hydrocephalus because of occlusion of the aqueduct. No subarachnoid fluid was found supratentorially, and there was a well defined pressure cone.

Metastatic tumor was seen grossly in the liver, kidneys, ribs, vertebrae, left ovary, and adrenal (Fig. 6 and 7).

Microscopically, the tumor presented the characteristic neuroepithelial rosettes (Fig. 8) with abundant foci of necrosis and calcification. The subarachnoid seedings also contained calcifications secondary to tumor cell necrosis.

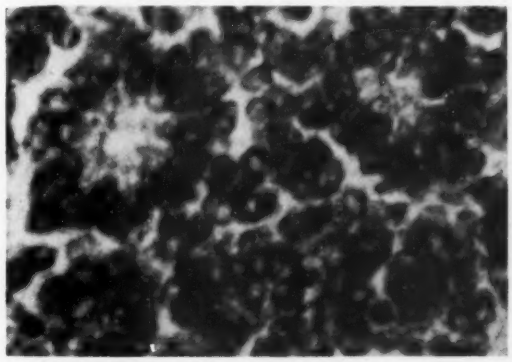


Fig. 8. Photomicrograph of tumor showing characteristic neuroepithelial rosettes (400×).

SUMMARY

A case of retinoblastoma with extension to the brain and subarachnoid seeding is described. Numerous diffuse intracerebral calcifications were seen roentgenographically, though no calcification could be seen in the orbit.

Lawrence A. Davis, M.D.
Children's Hospital
226 East Chestnut Street
Louisville, Kentucky

REFERENCES

1. Caffey, J. Pediatric X-ray Diagnosis. Third Edition. Year Book Publishers, Inc., Chicago, 1956.
2. Haymaker, W., and others. Cerebral involvement with advanced periventricular calcification in generalized cytomegalic inclusion disease in newborn. *J. Neuropath. & Exper. Neurol.*, 1954, *13*, 562–586.
3. Manchester, P. T., Jr. X-ray diagnosis of orbital tumors. *South. M. J.*, 1954, *47*, 231–234.
4. Merriam, G. R., Jr. Retinoblastoma; analysis of seventeen autopsies. *Arch. Ophth.*, 1950, *44*, 71–108.
5. Pfeiffer, R. L. Roentgenography of exophthalmos with notes on roentgen ray in ophthalmology. *Am. J. Ophth.*, 1943, *26*, 724–741; 816–833; 928–942.
6. Pfeiffer, R. L. Roentgenographic diagnosis of retinoblastoma. *Arch. Ophth.*, 1936, *15*, 811–821.
7. Swan, K. C., and Hyman, S. Experiences with tumors of retina. *Arch. Ophth.*, 1952, *47*, 416–424.

ROENTGEN APPEARANCES OF THE LUNGS IN 1,000 APPARENTLY NORMAL FULL TERM NEWBORN INFANTS*

By JEROME NADELHAFT, M.D., *and* KENT ELLIS, M.D.
NEW YORK, NEW YORK

CONSIDERING the recent interest in the respiratory physiology and pathology of the newborn infant, we thought it would be worthwhile to present a summary of the pulmonary findings on chest roentgenograms of apparently normal full term infants taken in the first four days after birth. This group of 1,000 is of particular interest because all the babies were very carefully evaluated clinically and were followed for at least one year.

MATERIAL

In October, 1946, a study was undertaken by members of the Departments of Obstetrics and Pediatrics of Presbyterian Hospital to determine the relationship of maternal infections and other illnesses occurring during pregnancy to the incidence of abortion, stillbirths, prematurity, infantile deaths and congenital malformations.[7] Included in the investigation were all expectant mothers admitted to the antepartum clinic with a duration of pregnancy of four months or less at the first visit. As a result of 5,964 pregnancies, 6,055 individuals were born. A single posteroanterior erect chest roentgenogram was taken of each newborn, usually within the first few days of life. We reviewed the films and clinical data of 1,366 consecutive cases of this series. A group of 1,000 was chosen for study on the basis of the following criteria: (a) Minimum birth weight of 2,500 gm.; (b) asymptomatic uncomplicated postnatal period; (c) absence of any significant cardiorespiratory abnormality as determined by careful histories and physical examinations done in the neonatal period and again at six and twelve months; and (d) technically satisfactory chest roentgenogram taken within the first four days after the day of birth.

ROENTGENOGRAPHIC TECHNIQUE

All films were exposed at a target-film distance of six feet, in the posteroanterior erect position. The infant's arms were extended and held at the sides of his head. The exposure factors were 68 kv., 100 ma., 1/20 sec. An effort was made to expose the film at the beginning of a cry to record the appearance of the thorax, as far as possible, in inspiration. The day after birth on which a patient was roentgenographed was determined by convenience.

TECHNIQUE OF INTERPRETATION AND RESULTS

The films were reviewed by both authors in concert, and the appearances of the lung fields, diagrammatically depicted in Figure 1, were classified as follows:

Class I. Radiolucent lung fields without prominent pulmonary markings or focal areas of increased density, found in 71 per cent (Fig. 2).

Class II. Generalized mild increase in pulmonary density or markings of fine, coarse or mixed pattern, found in 24 per cent (Fig. 3).

Class III. Generalized moderate increase in pulmonary markings, or density, definitely outside the usual range, found in 1–2

* From the Department of Radiology of the College of Physicians and Surgeons of Columbia University and the Radiological Service of the Presbyterian Hospital, New York, New York.

Aided by grants from the Rockefeller Foundation, the New York Foundation, the Life Insurance Medical Research Fund, the Association for the Aid of Crippled Children, the New York State Department of Health, and the United States Public Health Service grant RG-4194.

These roentgenograms are part of a larger study of newly born infants at the Babies and Sloane Hospitals, New York, New York, directed by Dr. Rustin McIntosh.

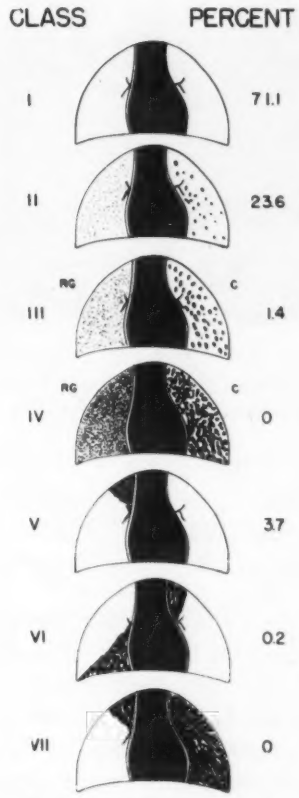


Fig. 1. Classification and percentage distribution of lung appearances in 1,000 clinically normal newborn infants. (RG = reticulogranular pattern; C = coarse pattern.)

per cent. This class was divided into three subgroups: cases in which the markings were coarse and flocculent (Fig. 4), those with fine, reticulogranular markings (Fig. 5), and those showing a mixed pattern (Fig. 6).

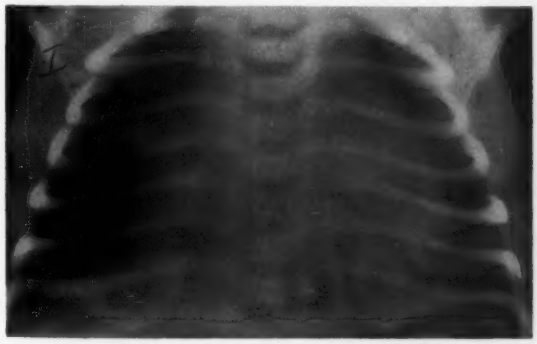


Fig. 2. Class I. Radiolucent lung fields without prominent pulmonary markings or focal areas of increased density.

Fig. 3. Class II. Mild, generalized increase in pulmonary density or markings of fine, coarse, or mixed pattern.

Class IV. Generalized marked increase in pulmonary density or markings, not found in any case in this study.

Class V. Local increased pulmonary density in a region smaller in area than one-half of one lung field, found in 3–4 per cent (Fig. 7).

Class VI. Local increased pulmonary density in a region or regions corresponding in area to more than one-half but less than one whole lung field, found in less than 1 per cent (Fig. 8).

Class VII. Local increased pulmonary density in region larger than one lung field, not found in any case in this study.

In the few cases where a segmental opacity was associated with a generalized increase in pulmonary density, the roentgenogram was classified in the latter category. Special attention was given to cer-

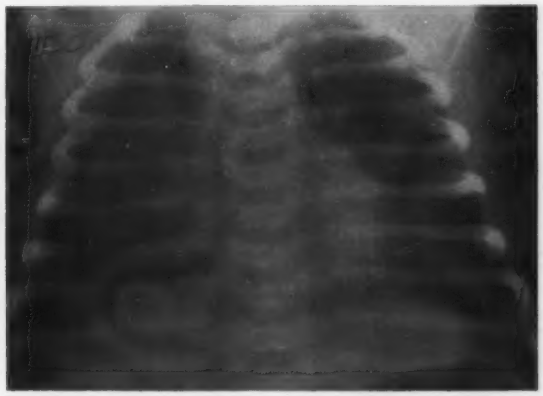


Fig. 4. Class III C. Coarse type of moderate generalized increase in pulmonary markings.

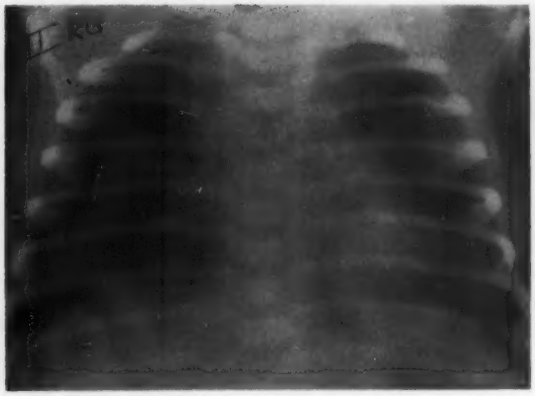


FIG. 5. Class III RG. Reticulogranular type of moderate, generalized increase in pulmonary markings.

tain features. The bronchial air shadows were only occasionally seen distal to the two main bronchi. Even then, these lucencies could not easily be traced peripherally into the lung fields, and the margins of these air columns were indistinct. In the majority of Class II and in all of the Class III roentgenograms, the boundaries of the heart shadow were not as well defined as in Class I; this observation was made more often on the right side. Occasionally, a focal area of increased radiolucency was noted, but only one pneumothorax was seen in this group of asymptomatic patients. Gross pleural effusions were not found, but a lung fissure was visible in 14 per cent.

Of the 14 cases in Class III (generalized increase in pulmonary markings, definitely outside the usual range), 8 had a predominantly flocculent pattern, 4 a fine, reticulo-

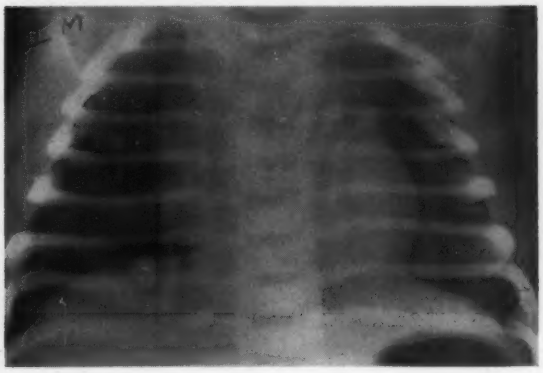


FIG. 6. Class III. Mixed type of moderate, generalized increase in pulmonary density.

FIG. 7. Class V. Local increased pulmonary density in a region smaller in area than one half of one lung field. In this case, the right lower lung field is involved.

granular pattern, and two a mixed pattern. Again, in this class, the segmental bronchial air shadows were not discernible.

DISCUSSION

The borderlines between adjacent classes in this study, but particularly between Class I and Class II, were not sharp. Table I demonstrates that more than 90 per cent of the roentgenograms were classified as either Class I or II, and that this distribution did not vary significantly during the first four days after birth. Birth weight also had no influence on this distribution.

Classes III to VII, which included 5 per cent of the cases, were characterized by images of increased density that were sufficiently striking to be considered possible evidence of pulmonary pathology. We can-

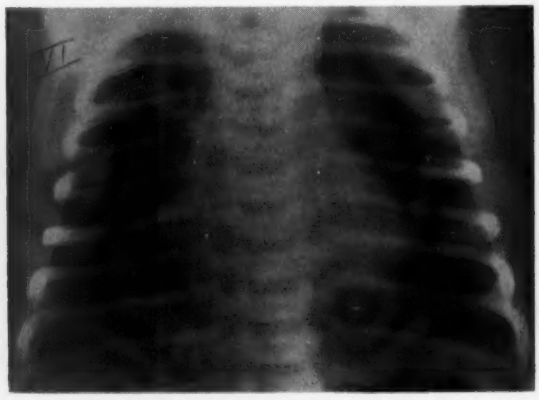


FIG. 8. Class VI. Local increased pulmonary density in a region or regions corresponding in area to more than one half but less than one lung field. In this case, both upper lung fields are involved.

TABLE I

DISTRIBUTION OF LUNG APPEARANCES IN RELATION TO DAY AFTER BIRTH ON WHICH ROENTGENOGRAM WAS MADE

Day after Birth	Percentage of Cases		Total Number of Cases
	Classes I and II Combined	All Other Classes Combined	
1	94%	6%	340
2	93%	7%	361
3	96%	4%	220
4	97%	3%	79

not tell whether these images were due to primary lack of aeration or to subclinical morbid processes that appeared in previously well aerated lungs, since we have no serial chest films starting at the time of birth. Such sequential films in as large a series of clinically normal newborns as ours would help resolve a controversy about the origin of these shadows. Certain investigators[1,2,3,5,6,9,11,12] reported that, in some cases, roentgenographic images of increased density, which they interpreted as evidence of incomplete expansion or physiologic atelectasis, persist for several days. On the other hand, others[4,8,10] stated that aeration is roentgenographically complete within a few minutes or hours after birth.

In this paper, we have defined by means of classification the range of variation in the roentgen appearances of the lungs in clinically normal full term infants. Having this information, the radiologist is able more intelligently to evaluate the significance of the densities he sees on the chest roentgenograms of newborn babies.

SUMMARY

We reviewed the chest roentgenograms of 1,000 normal full term newborn infants made within the first four days after the day of birth and classified the appearances of the lungs. In a small percentage of the cases, 5 per cent, images of increased density occurred that could be interpreted as evidence of significant intrapulmonary disease.

Jerome Nadelhaft, M.D.
622 West 168th Street
New York 32, New York

We wish to thank Dr. John Caffey for his advice and encouragement.

REFERENCES

1. Caffey, J. Pediatric X-ray Diagnosis. Third edition. Year Book Publishers, Inc., Chicago, 1956, pp. 269–270.
2. Davis, C. H., and Stevens, G. W. Value of routine radiographic examination of newborn based on study of 702 consecutive babies. *Am. J. Obst. & Gynec.*, 1930, *20*, 73–76.
3. Dunham, E. C., and D'Amico, M. Roentgenographic study of thoraces of newborn infants. *Yale J. Biol. & Med.*, 1934, *6*, 385–401.
4. Farrell, J. T., Jr. Roentgen appearance of chest of newborn infants. Am. J. Roentgenol. & Rad. Therapy, 1930, *24*, 140–146.
5. Lantuejoul, P., Ribadeau-Dumas, L., and Herraux. Roentgen images of lung and digestive tract at birth. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1948, *64*, 161–166.
6. Mayer, M. Study of pulmonary expansion at birth by serial radiography (170 cases). *Bull. Féd. Soc. gynéc. et obst.*, 1952, special supplement to Vol. *4*, 279–282.
7. McIntosh, R., Merritt, K. K., Richards, M. R., Samuels, M. H., and Bellows, M. T. Incidence of congenital malformations: Study of 5,964 pregnancies. *Pediatrics*, 1954, *14*, 505–522.
8. Peterson, H. G., Jr., and Pendleton, M. E. Contrasting roentgenographic pulmonary patterns of hyaline membrane and fetal aspiration syndromes. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1955, *74*, 800–817.
9. Solis-Cohen, L., and Bruck, S. Roentgen examination of chest of 500 newborn infants for pathology other than enlarged thymus. *Radiology*, 1934, *23*, 173–179.
10. Steiner, R. E. Radiology of respiratory distress in newborn. *Brit. J. Radiol.*, 1954, *27*, 491–499.
11. Wasson, W. W. Roentgenographic study of infant chest as seen at birth. *J.A.M.A.*, 1924, *83*, 1240–1243.
12. Weymuller, C. A., Bell, A. L. L., and Krahulik, L. Roentgenographic changes in thorax of normal newborn babies. *Am. J. Dis. Child.*, 1928, *35*, 837–855.

ROENTGENOGRAPHIC FINDINGS IN HYALINE MEMBRANE DISEASE IN INFANTS WEIGHING 2,000 GRAMS AND OVER*

By KENT ELLIS, M.D., *and* JEROME NADELHAFT, M.D.
NEW YORK, NEW YORK

RESPIRATORY distress, whether due to hyaline membranes, aspiration, infection, pulmonary hemorrhage, cardiac dysfunction or cerebral damage, is one of the most important clinical problems of the neonatal period. The neonatal respiratory disorder which has provoked the most recent interest is hyaline membrane disease. In the present paper the roentgenographic findings in the lungs of 7 babies who at necropsy had hyaline membrane disease are compared with those of normal infants, of infants with other pulmonary diseases, and of infants who recovered from respiratory distress syndromes.

Clinically, severe respiratory distress with marked retractions of the sternal and costal margins is usually found in hyaline membrane disease. At necropsy, in the severe case, the lungs are of uniform dark purple color and sink when placed in water. Microscopically, the alevoli are characteristically atelectatic, and the frequently overdistended alveolar ducts are lined with rather amorphous eosinophilic material.[2] Hyaline membranes are apparently not seen in the lungs of stillborn infants and are rarely found in infants dying less than two hours after birth. Nearly all deaths believed to be related primarily to this condition occur during the first four days after birth. After the thirty-sixth hour the incidence of superimposed pneumonitis becomes relatively high. The syndrome is more common in premature infants and in those delivered by cesarean section.[8]

MATERIAL AND RESULTS

Except in 2 cases of hyaline membrane disease and in several other instances when the babies were extremely sick, all roentgenograms were made with the patients erect, using the technique described previously.[6]

I. HYALINE MEMBRANE DISEASE

The necropsy files of Babies Hospital for the period 1942–1955 contained 7 cases that fulfilled these criteria:

A. Atelectasis and hyaline membranes were the major findings in the lungs at necropsy.
B. Birth weight was 2,000 grams or more.
C. Antemortem chest roentgenograms were available that were satisfactory for interpretation of the lungs. (Five cases were rejected because of unsatisfactory films. In one of these a massive pneumothorax compressed and obscured the lungs.)
D. Death occurred within four days after birth.

Roentgenographic Appearance of the Lungs. In all 7 cases a generalized marked increase in pulmonary density was seen. This increased density appeared to be composed of many tiny punctate and some linear images producing a pattern that can be described as finely granular or even reticulogranular.[7] In all these cases, contrary to our observations in normal infants,[6] the bronchial air shadows could be seen extending far peripherally into the lungs. Peripheral radiolucencies measuring up to 2 mm. in diameter were distinctly seen in 4 cases.

The generalized granular increase in pulmonary density described in the present cases corresponds to the lung appearance

* From the Department of Radiology of the College of Physicians and Surgeons of Columbia University and the Radiological Service of the Presbyterian Hospital, New York, New York.

of the reticulogranular type, Class IV, in the classification we have devised for newborn infants.[6] This marked degree of granular increase in density was not found in our groups of normal controls.

REPORT OF CASES

Case I. Unit no. 210719. This Negro male weighed 2,000 gm. when delivered by repeat cesarean section after premature onset of labor at thirty-six weeks. Respiratory distress with retractions and periods of apnea started immediately after birth. A chest roentgenogram at two hours after birth showed a generalized granular pattern of marked increase in pulmonary density (Class IV appearance). The bronchial air shadows were strikingly evident (Fig. 1). Despite treatment with oxygen, warm humid atmosphere, antibiotics, stimulants and gastric aspiration, death occurred at eighteen hours.

Case II. Unit No. 100646. This white male weighed 2,600 gm. following normal vaginal delivery at term. Cyanosis and subcostal retractions began two hours after birth. A roentgenogram made at thirty-three hours demonstrated a generalized granular pattern of marked increase in lung density (Class IV appearance), as well as conspicuous bronchial air shadows and many small peripheral radiolucencies (Fig. 2). Despite treatment with oxygen, warm humid atmosphere, antibiotics, and gastric aspiration, this baby experienced increasing respiratory difficulty and died at ninety-two hours.

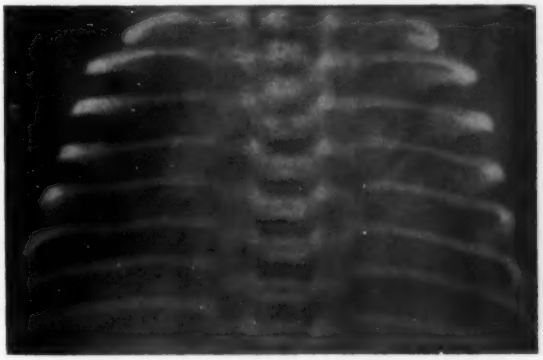


Fig. 1. Case I. Hyaline membrane disease. A generalized granular pattern of marked increase in pulmonary density is associated with conspicuous bronchial air shadows. This roentgenogram was made two hours after birth and sixteen hours before death.

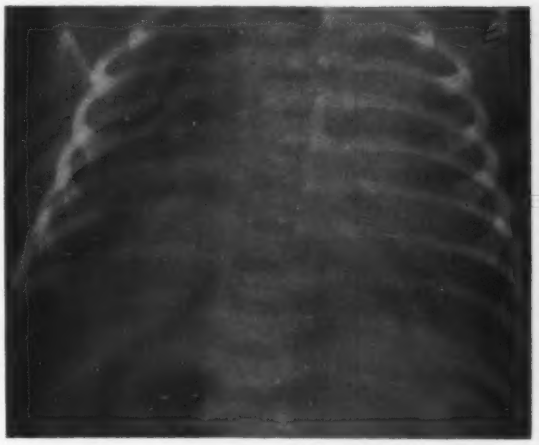


Fig. 2. Case II. Hyaline membrane disease. A generalized granular pattern of marked increase in pulmonary density is associated with conspicuous bronchial air shadows and with many small peripheral radiolucencies. This roentgenogram was made thirty-three hours after birth and fifty-nine hours before death.

Case III. Unit No. 088157. This white female weighed 2,100 gm. after a rapid vaginal delivery following premature rupture of membranes at thirty-three weeks. Respiratory distress began immediately with retractions and grunting respiration. A chest roentgenogram at eighteen hours demonstrated a generalized granular pattern of marked increase in pulmonary

Fig. 3. Case III. Hyaline membrane disease. A generalized granular pattern of marked increase in pulmonary density is associated with conspicuous bronchial air shadows and with many small peripheral radiolucencies. This roentgenogram was made eighteen hours after birth and six hours before death.

density (Class IV appearance), prominent bronchial air shadows and multiple tiny radiolucencies in the midlung fields (Fig. 3). Despite treatment with oxygen, warm humid atmosphere, antibiotics and stimulants, death ensued at twenty-four hours.

CASE IV. Unit No. 103861. This white male weighing 2,500 gm. was delivered by elective repeat cesarean section at another hospital. After several hours, respiratory distress with retractions and episodes of cyanosis were noted. A roentgenogram at twenty-eight hours showed a generalized granular pattern of marked increase in pulmonary density (Class IV appearance), prominent bronchial air shadows and a number of tiny round radiolucencies in the midlung regions. Despite usual treatment, progressively more severe respiratory distress terminated in death at sixty-eight hours.

CASE V. Unit No. 121019. This Negro female weighing 2,400 gm. was delivered by repeat cesarean section after premature onset of labor at thirty-three weeks. Respiratory distress with cyanosis and costal retractions was observed soon after birth. A roentgenogram at twenty-two hours revealed a generalized granular pattern of marked increase in density (Class IV appearance), a few tiny round lucencies in the midlung fields, and moderately good demonstration of the segmental bronchial lumina. Despite usual treatment, including tracheal aspiration, death took place at twenty-four hours.

CASE VI. Unit No. 121463. This white female weighing 2,600 gm. was born by normal vaginal delivery at 35 weeks. The moderate cyanosis noted at birth was relieved by oxygen, but progressive respiratory distress with retractions followed. A roentgenogram at twenty-four hours showed a generalized granular pattern of marked increase in pulmonary density (Class IV appearance) and an extensive network of bronchial air shadows. Despite usual measures, death occurred at thirty hours.

CASE VII. Unit No. 110341. This white female weighed 2,400 gm. after a normal vaginal delivery at thirty-six weeks. Marked retractions and periods of apnea occurred soon after birth, but temporary improvement followed treatment with oxygen, warm humid atmosphere and antibiotics. A roentgenogram at twenty-five hours revealed a generalized granular pattern of marked increase in pulmonary density (Class IV appearance) and demonstrated well the major and segmental bronchial air shadows. Never free of retractions and gradually losing ground clinically, this baby died at seventy-eight hours despite laryngoscopic aspiration terminally.

II. CONTROL GROUPS

Control cases were considered in the following groups: clinically normal infants, infants with necropsy proved pulmonary disease other than hyaline membrane disease, and infants who recovered from respiratory distress syndromes.

Group A. Clinically Normal Infants. The chest roentgenograms of 1,000 clinically normal full term infants described in the preceding paper[6] served as controls for cases of hyaline membrane disease with birth weights of 2,500 gm. or more. The roentgenograms were all taken in the first four days after birth.

In the same population of 1,366 infants from which the 1,000 control infants mentioned above were obtained, there were 59 infants with birth weights of 2,000 to 2,500 gm. who, except for weight, fulfilled the same criteria that were required for inclusion in the control group of heavier term infants. The lungs as shown on the chest roentgenograms of these 59 infants were classified in the same manner as those of the term infants. In 43 cases (73 per cent) the lung fields were normally radiolucent (Class I); in 14 cases (24 per cent) a mild generalized increase in pulmonary markings or density was present (Class II); in 1 case a generalized granular pattern of moderate increase in pulmonary density was seen (Class III), but bronchial air shadows were not visible; and in 1 case a segmental area of increased pulmonary density was observed (Class V). The distribution of the lung appearances in this group of clinically normal infants weighing 2,000 to 2,500 gm. was not significantly different than that of the term group.

Because we had no suitable controls for infants weighing less than 2,000 gm. at

birth, no case of hyaline membrane disease in this weight range was included in the study.

Roentgenographic Appearance of the Lungs. Neither the generalized granular pattern of marked increase in pulmonary density (Class IV appearance) nor the marked prominence of the bronchial air shadows described above in hyaline membrane disease was seen in any of the roentgenograms of these clinically normal infants weighing 2,000 gm. and over.

Group B. Infants with Necropsy Proved Pulmonary Diseases Other Than Hyaline Membrane Disease. Cases were selected from the necropsy files of Babies Hospital for the period 1942–1955 which had the following characteristics:

A. Acquired pulmonary disease other than hyaline membrane disease such as hemorrhage, pneumonia, atelectasis, or aspiration of amniotic fluid, singly or in combination, was a major finding at necropsy.

B. Birth weight was 2,000 gm. or more.

C. Antemortem chest roentgenograms were available that were made during the first four days of life and that were satisfactory for interpretation of the lung appearances.

D. Death occurred within seven days after birth.

Roentgenographic Appearance of the Lungs. In none of the 24 cases falling into this group was there demonstrated that combination of a generalized granular pattern of marked increase in pulmonary density and distinctly defined segmental bronchial air shadows which might be confused with what has been described above in hyaline membrane disease.

Group C. Infants Who Recovered from Clinical Respiratory Distress Syndromes. Roentgenograms taken during the first four days after birth were available on 64 infants with birth weights of 2,000 gm. or more, who had clinical neonatal respiratory distress and who recovered. The respiratory distress was manifested by combinations of cyanosis, periods of apnea or hyperpnea, grunting respirations and retractions.

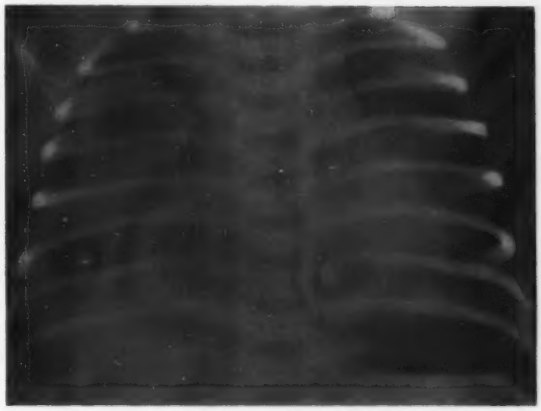


Fig. 4. Case VIII. Respiratory distress syndrome. A generalized granular pattern of marked increase in pulmonary density is associated with fair demonstration of bronchial lumina. This roentgenogram was made ninety-six hours after birth. The patient recovered.

Roentgenographic Appearance of the Lungs. Though they varied from the definitely normal to the grossly abnormal, only in 3 cases, illustrated in Figures 4, 5 and 6, did the lung appearances resemble that described above in hyaline membrane disease.

REPORT OF CASES

Case VIII. Unit No. 131279. This white female weighing 2,700 gm. was delivered by repeat elective cesarean section for cephalopelvic disproportion at thirty-six weeks. Within five hours, the baby displayed grunting respirations and retractions, and was cyanotic when out of oxygen. Treatment with warm humid atmosphere, oxygen and antibiotics was accompanied by gradual improvement. A roentgenogram at ninety-six hours revealed a generalized granular pattern of marked increase in lung density (Class IV appearance), but the bronchial air shadows, though seen, were not as well demonstrated as in the cases of hyaline membrane disease (Fig. 4). This baby was discharged well on the fourteenth day.

Case IX. Unit No. 171119. This white female weighing 3,300 gm. was delivered by elective cesarean section at thirty-six weeks because of maternal history of four abortions, a stillbirth and a neonatal death. Respiratory distress with

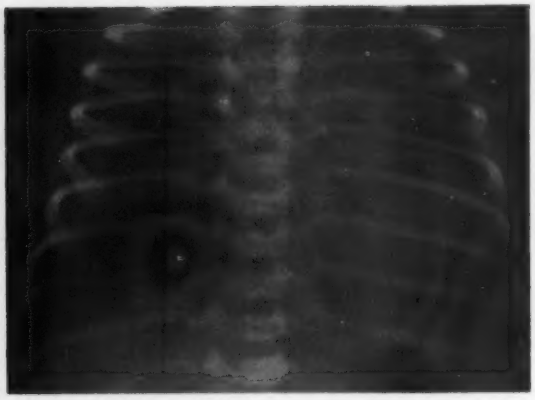


FIG. 5. Case IX. Respiratory distress syndrome. A generalized granular pattern of marked increase in pulmonary density is associated with moderately prominent bronchial lumina. This roentgenogram was made twenty-four hours after birth. The patient recovered.

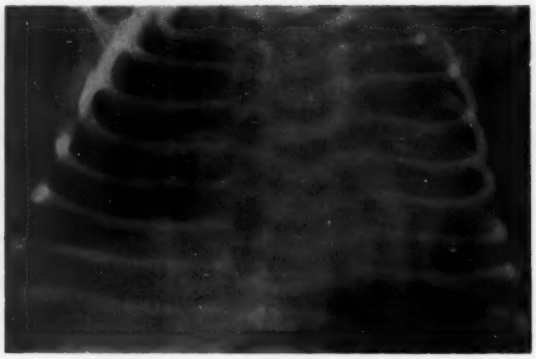


FIG. 6. Case X. Respiratory distress syndrome. A generalized granular pattern of marked increase in pulmonary density is associated with fair demonstration of bronchial lumina which are best seen below the diaphragmatic domes. This roentgenogram was made thirty hours after birth. The patient recovered.

costal retractions and cyanosis began immediately after birth. Gradual improvement followed treatment with warm humid atmosphere, oxygen, and antibiotics. A roentgenogram at twenty-four hours revealed a generalized granular pattern of marked increase in density (Class IV appearance) and moderately prominent bronchial air shadows (Fig. 5). The infant was discharged, improved, at ten days.

CASE X. Unit No. 837760. This white male weighing 2,250 gm. was born by precipitous vaginal delivery at thirty-six weeks. On the day of delivery, the mother was acutely ill with pneumonia and perhaps an upper urinary tract infection for which antibiotics were given. During the first hour, the baby had several cyanotic episodes. Subcostal retractions soon became obvious. Treatment with warm humid environment, oxygen and antibiotics was accompanied by slow recovery over the next two weeks. A roentgenogram at thirty hours disclosed a generalized granular pattern of marked increase in density (Class IV appearance) and a fair demonstration of segmental bronchial air shadows (Fig. 6). Roentgenograms at five, ten and fifteen days showed gradual improvement. The child has had several episodes of bronchopneumonia in the subsequent eight years, although a recent chest roentgenogram is unremarkable.

DISCUSSION

Between the time a chest roentgenogram is made and the time a lung is examined pathologically, an appreciable interval usually elapses during which, particularly in rapidly changing processes such as we have been considering, an indeterminate but significant alteration may take place in the lung. This limitation on the correlation that can be made between anatomic and roentgen findings in pulmonary disease should be borne in mind during the discussion that follows.

In our cases of hyaline membrane disease, the roentgenographic finding of a generalized granular pattern of marked increase in pulmonary density is consistent with the microscopic finding of widespread alveolar atelectasis reported by Latham *et al.*[5] in 42 cases of severe uncomplicated hyaline membrane disease. The unusually prominent bronchial air shadows express the roentgenographic contrast between the air-distended bronchi and the dense atelectatic lung parenchyma. A similar explanation probably accounts for the small peripheral rounded radiolucencies which were seen in 4 of our 7 cases and which may correspond to the overdistended alveolar ducts and respiratory bronchioles described histologically by Claireaux.[2]

Donald and Steiner[3] as well as Peterson and Pendleton[7] have associated the roentgen demonstration of a generalized granular pattern of increase in pulmonary density with hyaline membrane disease in newborn

infants experiencing respiratory distress. Both of these groups of authors have also pointed out that in many such cases the bronchial air shadows are unusually clearly seen, especially in the mid and lower lung fields. Both the generalized granular pattern of marked increase in density and the conspicuous bronchial lumina were present on the chest roentgenograms of each of the 7 examples of hyaline membrane disease reported in the present paper.

Roentgenologically, Donald and Steiner[3] described three stages in the evolution of hyaline membrane disease:

1. First, there appears a fine miliary mottling throughout the lung fields.

2. This is followed in the progressive lesion by a coarser and more coalescent type of opacity. At this stage the bronchial tree is often clearly demarcated.

3. Finally, the shadows become confluent as a result of lobar or lobular consolidation and collapse.

If their "coarse and more coalescent type of opacity" is considered a verbal variation that is roentgenographically equivalent to our "generalized granular pattern of marked increase in density," then, because the bronchial lumina were always distinctly shown, all our cases fall into group 2 of this classification, and none into groups 1 and 3. The lack of serial roentgenograms in our material could account for this situation, and consequently we can neither confirm nor contest their concept of the evolution of the disease.

On the roentgenograms of some of our asymptomatic controls, a granular pattern of increased density was present but never to the very marked degree exhibited in hyaline membrane disease. The outline of the bronchial tree was never nearly as well demonstrated as in the cases of hyaline membrane disease.

In none of our control cases of infants who died with necropsy evidence of significant pulmonary disease other than hyaline membrane disease were we able to find the combination of a generalized pattern of marked increase in density and conspicuous bronchial air shadows. Donald and Steiner[3] reported 4 infants in whom no hyaline membranes were found at necropsy although "radiologic signs (were) present" on premortem films. In 1 of these cases, the absence of prominent bronchial air shadows was specifically mentioned, while in the other 3 cases no specific remark was made concerning the bronchi.

Only in the control group of babies who recovered from respiratory distress did we find the 3 cases in which the lung findings closely resembled those of hyaline membrane disease. These may have been examples of a nonlethal form of the disease.

It is well recognized that other intrapulmonary morbid conditions besides atelectasis, such as hemorrhage, pneumonia, edema, and the effects of aspirated material produce images of increased density on the chest roentgenograms of newborn infants. Landing[4] has pointed out that these conditions are often found in varying combinations in conjunction with hyaline membranes and atelectasis in the lungs of infants dying of respiratory distress syndromes. Therefore, we do not wish to imply that the pulmonary densities we have described in the roentgenograms of cases of hyaline membrane disease are due exclusively to atelectasis.

It is to be emphasized that our data and conclusions concern only babies weighing more than 2,000 gm. and they are not necessarily applicable to infants weighing less than 2,000 gm., who constitute the majority of patients with hyaline membrane disease.

SUMMARY

We reviewed the chest roentgenograms of 7 babies weighing 2,000 gm. or more who, having experienced respiratory distress, died during the first four days following birth and who at necropsy had relatively uncomplicated combinations of alveolar atelectasis and hyaline membranes in the lungs. On all of these roentgenograms, a generalized granular pattern of marked increase in pulmonary density was found to be associated with demonstrable bronchial air shadows that were unusual both in

sharpness of outline and in their peripheral extension into the lungs.

These roentgen features reflect the gross manifestations of the histologic changes found in severe hyaline membrane disease, particularly the generalized alveolar atelectasis; they do not represent the hyaline membranes.

Among control roentgenograms of infants of comparable age and weight drawn from necropsied cases with other pulmonary diseases, from a large population of asymptomatic babies and from a series of infants who recovered from respiratory distress syndromes, only 3 cases—all from the last group—were found in which the lung appearance closely resembled that just described in hyaline membrane disease. These cases may have been examples of a nonlethal form of hyaline membrane disease.

In our experience, the roentgen appearance of a generalized granular pattern of marked increase in pulmonary density combined with unusually conspicuous bronchial air shadows on chest roentgenograms of infants with respiratory distress in the first days of life was characteristic of hyaline membrane disease.

Kent Ellis, M.D.
622 West 168th Street
New York 32, New York

We wish to thank Dr. John Caffey for his advice and encouragment and Dr. William Blanc for reviewing the histologic sections of the cases of hyaline membrane disease.

REFERENCES

1. Blystad, W., Landing, B. H., and Smith, C. A. Pulmonary hyaline membranes in newborn infants. Statistical, morphologic and experimental study of their nature, occurrence and significance. *Pediatrics*, 1951, *8*, 5–21.
2. Claireaux, A. E. Hyaline membrane in neonatal lung. *Lancet*, 1953, *2*, 749–753.
3. Donald, I., and Steiner, R. E. Radiography in diagnosis of hyaline membrane. *Lancet*, 1953, *2*, 846–849.
4. Landing, B. H. Pathologic features of respiratory distress syndromes in newborn infants. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1955, *74*, 796–799.
5. Latham, E. F., Nesbitt, R. E. L., Jr., and Anderson, G. W. Clinical pathological study of newborn lung with hyaline-like membranes. *Bull. Johns Hopkins Hosp.*, 1955, *96*, 173–198.
6. Nadelhaft, J., and Ellis, K. Roentgen appearances of lungs in 1,000 apparently normal full term newborn infants. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1957, *78*, 440–443.
7. Peterson, H. G., Jr., and Pendleton, M. E. Contrasting roentgenographic pulmonary patterns of hyaline membrane and fetal aspiration syndromes. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1955, *74*, 800–817.
8. Potter, E. L. Pathology of the Fetus and the Newborn. Year Book Publishers, Inc., Chicago, 1952.

Vol. 78, No. 3

ROENTGEN STANDARDS FOR SIZE OF THE PITUITARY FOSSA FROM INFANCY THROUGH ADOLESCENCE*

By FREDERIC N. SILVERMAN, M.D.
CINCINNATI, OHIO

IN THE third edition of his text book "Pediatric X-Ray Diagnosis" published in 1956, Caffey[1] repeats a statement made in previous editions that "there is little factual basis for a belief that the pituitary fossa is significantly altered in disease other than those associated with expanding lesions of the hypophysis and some types of increased intracranial pressure." In this attitude Caffey supports the work of Gordon and Bell,[6] Camp,[2] and others,[3,11,12] who previously had reached the conclusion that the extreme variations of pituitary size in health precluded recognition of disease by roentgen examination of the pituitary fossa. Others[7,8,10,13] have remarked on enlargement in association with cretinism to a degree which suggested that a relationship did, at times, exist between hypothyroidism and recognizable enlargement of the pituitary fossa. The observation of what appeared to be large pituitary fossae in untreated hypothyroid children impelled us to consult the standards on which these divergent opinions were based.

It became progressively clear that, except for Francis' study,[5] available standards did not provide information on the extreme range of normal as determined from samples of adequate size. Gordon and Bell,[6] for example, examined only 104 children between the ages of one and twelve years. In no single age group were there more than 13 children and in some as few as 3. Royster and Rodman[13] examined 350 lateral skull roentgenograms of children, but their report did not include their basic data and ranges of the several dimensions are not given. Camp's[2] study of 500 skull roentgenograms was restricted to adults. Hare and co-workers'[8] measurements of approximately 700 roentgenograms provided areas rather than linear measurements, but age intervals were great, no considerations were given to sex differences except in persons over sixteen years of age, and the number of observations on which the means are based was not indicated. Other reports[10] are comparable in defining the "normal" in terms of the central tendency rather than the range.

In addition, there has not been agreement on the dimensions to be measured (Fig. 1). Some authors[11] measured the

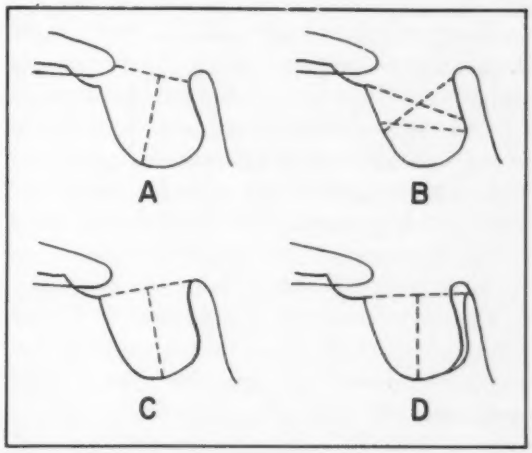


FIG. 1. Methods of measuring pituitary fossa. (*A*) "Length" is interclinoid distance; "depth" is perpendicular dropped from this line. (*B*) Several techniques used for measurement of "greatest (apparent) length": tuberculum to most remote point on posterior wall; tip of dorsum to most remote point on anterior wall; region of middle clinoids to most remote point on posterior wall. (*C* and *D*) are examples of technique used in this study. "Length" corresponds to position of diaphragma sellae, and "depth" is perpendicular dropped to deepest point.

* From the Departments of Pediatrics and Radiology, College of Medicine, University of Cincinnati; The Children's Hospital and Children's Hospital Research Foundation, Cincinnati; and The Fels Research Institute, Antioch College, Yellow Springs, Ohio. Presented in part at the VIII International Congress of Paediatrics, Copenhagen, Denmark, July 22–27, 1956.

"length" as the greatest anteroposterior dimension of the pituitary fossa. In such measurements, no consideration is given to consistent orientation of the skull or of the sphenoid bone with respect to the horizontal and vertical planes, so that the diameters bear no constant relationship to anatomic landmarks. Others have measured the interclinoid distance as an indication of length, failing to recognize that the anterior clinoids, of which the shadows are projected onto the pituitary fossa, in no way enter into the formation of the membranous and bony enclosure for the pituitary gland. In several instances, the "depth" has been measured from the interclinoid line to the bottom of the projected fossa rather than from a line corresponding to the position of the diaphragma sellae.

Since measurement of the pituitary fossa can be assumed to reflect the size and perhaps the activity of the pituitary gland, the measurements should be related to landmarks which are anatomically contiguous to the pituitary body. Moreover, as the pituitary fossa in lateral projection varies appreciably in shape from individual to individual and in the same individual from time to time as a result of growth and development, an evaluation of the *area* subtended within its projected margins would appear to bear a closer relationship to pituitary gland size than simple linear dimensions. Karlas[9] in a monograph on the hypophyseal fossa in adults states that measuring the area of a sagittal section is preferable to the length and depth. He also measured the volume of the pituitary fossa by filling it with plasticene and found some correlation (but not strong) between the area of a sagittal mid-section and the volume. The area gave almost as good an idea of capacity as did the product of the length, depth, *and breadth.*

MATERIAL

At the Fels Research Institute in Yellow Springs, Ohio, a longitudinal study of normal child development has been in progress for approximately twenty years. In the course of this examination, lateral roentgenograms of the skull have been taken of the children under study at three-month intervals through the first year, at six-month intervals through the first seven years and at yearly intervals thereafter into adult life. This has made available for study a large group of roentgenograms providing both longitudinal and cross-sectional data with respect to the size of the pituitary fossa in different individuals at the same age, and in the same individual at different ages. Moreover, for each of the children examined, extensive biometric data are available so that relationships with respect to other somatic measurements and bodily functions can be studied if desired. The availability of this material made possible a study of pituitary fossa size which could answer the above objections. Meas-

TABLE I

MEAN AREA AND STANDARD DEVIATION OF PITUITARY FOSSA IN NORMAL BOYS, SHOWING AGE DISTRIBUTION OF POPULATION STUDIED

Age	N	Mean Area	Standard Deviation
1 mo.	109	19.1	5.7
3 mos.	98	23.7	5.1
6 mos.	104	31.5	7.7
9 mos.	89	36.2	7.2
1 yr.	94	42.5	7.5
1½ yrs.	81	46.2	7.0
2 yrs.	90	49.0	5.8
2½ yrs.	84	52.5	8.0
3 yrs.	94	54.2	8.4
3½ yrs.	87	55.2	7.4
4 yrs.	93	57.5	10.2
4½ yrs.	90	57.7	5.9
5 yrs.	93	59.8	2.8
5½ yrs.	83	61.6	9.2
6 yrs.	92	63.2	12.9
6½ yrs.	55	64.1	6.4
7 yrs.	88	65.7	9.1
8 yrs.	89	67.8	11.1
9 yrs.	87	67.8	4.3
10 yrs.	76	71.1	10.1
11 yrs.	69	70.4	9.3
12 yrs.	60	72.5	13.2
13 yrs.	52	73.5	5.7
14 yrs.	46	74.5	12.1
15 yrs.	42	76.9	10.6
16 yrs.	35	81.2	13.3
17 yrs.	31	81.0	11.3
18 yrs.	26	86.7	23.1

urements of area and of length (L) and depth (D) of the pituitary fossa were made on 2,137 roentgenograms from 168 boys and on 1,899 roentgenograms from 152 girls. The age distribution is shown in Tables I and II.

METHODS

Measurements of area were made with a compensating polar planimeter which gave direct readings of area in hundredths of square inches. Paired readings were made for each pituitary fossa and these had to agree within 0.01 square inch for the measurement to be acceptable. Conversion to the metric system (square millimeters) was made by multiplying by the factor 6.45. The area was measured by tracing the contour of the pituitary fossa from the tip of the dorsum sellae clock-wise to the tuberculum sellae and then following a straight line from the tuberculum sellae back to the point of origin (Fig. 1,*C* and *D*). This straight line corresponded to the position of the diaphragma sellae. In young children this was relatively simple as development of the posterior clinoid processes did not interfere with identification of the tip of the dorsum sellae (Fig. 2*A*). In older children the enlargement of the posterior clinoid processes frequently encroached on the projected shadow of the pituitary fossa (Fig. 2,*B* and *C*). This resulted in some instances in an actual decrease in the "area" with increasing age. In certain instances the tip of the dorsum sellae would be clearly visualized through the clinoid processes (Fig. 1*D* and 2*C*); in such instances the line of reference was drawn to this point and the tracing of the area was made with respect to the visual bony boundaries of the dorsum sellae disregarding the superimposition of the clinoid processes. Only lateral films were used for measurements; films in which recognizable obliquity could be demonstrated were discarded. Length and depth were measured using as a measurement of length (L) the distance from the dorsum sellae to the tuberculum sellae. In younger children this corresponded to the greatest anteroposterior diameter or exceeded the latter if the diameter was measured "within" the pituitary fossa. In older children the greatest anteroposterior diameter could occasionally be greater than this measurement because of the effect of the bulbous posterior clinoids. However, this measurement (L) did seem to offer a more standard line of reference for measurement than an arbitrarily selected greatest anteroposterior diameter and, therefore, was used exclusively.

A comparison was made between the length of the pituitary fossa determined by our technique and that of the "greatest (apparent) diameter" in 156 serial roentgenograms of 10 boys and 121 serial roentgenograms of 10 girls. The mean discrepancy in the boys' measurements was greater than in the girls':— 1.40 and +0.46 respec-

Table II

MEAN AREA AND STANDARD DEVIATION OF PITUITARY FOSSA IN NORMAL GIRLS, SHOWING AGE DISTRIBUTION OF POPULATION STUDIED

Age	N	Mean Area	Standard Deviation
1 mo.	75	21.2	7.0
3 mos.	73	25.2	7.0
6 mos.	73	31.7	2.8
9 mos.	70	35.8	4.8
1 yr.	73	38.0	7.4
1½ yrs.	73	42.6	8.4
2 yrs.	84	46.3	5.6
2½ yrs.	76	49.5	9.0
3 yrs.	80	50.1	8.7
3½ yrs.	86	52.5	5.2
4 yrs.	89	56.1	14.3
4½ yrs.	71	55.6	9.7
5 yrs.	86	56.9	10.4
5½ yrs.	62	59.0	15.9
6 yrs.	86	58.7	21.9
6½ yrs.	45	60.4	28.7
7 yrs.	91	60.3	25.0
8 yrs.	83	63.9	16.7
9 yrs.	72	64.0	6.9
10 yrs.	74	63.7	16.8
11 yrs.	71	64.6	10.1
12 yrs.	60	70.8	13.0
13 yrs.	61	74.9	14.7
14 yrs.	51	78.4	10.9
15 yrs.	42	78.6	15.8
16 yrs.	36	83.4	3.7
17 yrs.	28	86.5	21.8
18 yrs.	28	88.3	11.1

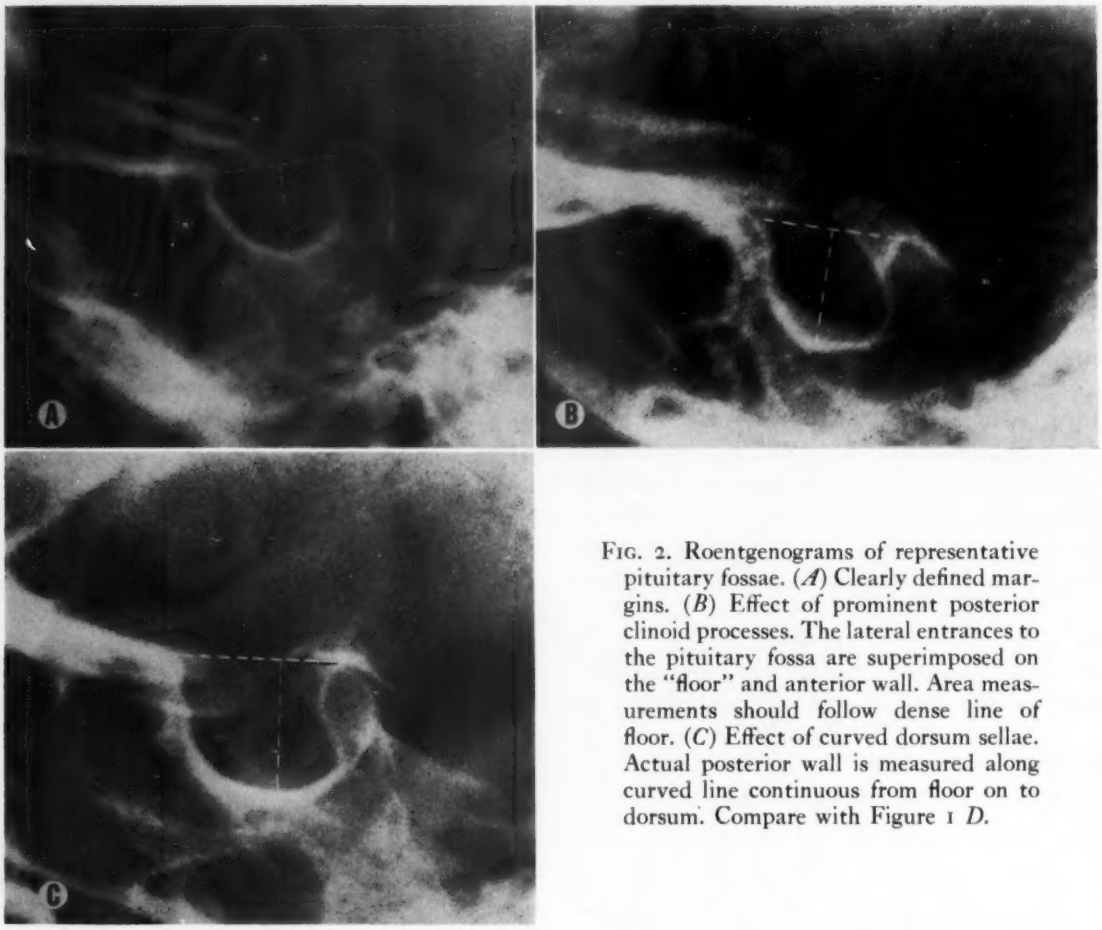


FIG. 2. Roentgenograms of representative pituitary fossae. (*A*) Clearly defined margins. (*B*) Effect of prominent posterior clinoid processes. The lateral entrances to the pituitary fossa are superimposed on the "floor" and anterior wall. Area measurements should follow dense line of floor. (*C*) Effect of curved dorsum sellae. Actual posterior wall is measured along curved line continuous from floor on to dorsum. Compare with Figure 1 *D*.

tively; the mean difference in the 277 measurements was −0.96 mm. in relation to our technique. From this it would appear that measurements of length from the tuberculum sellae to the tip of the dorsum sellae are on the average 1 mm. greater than those from the "greatest (apparent) diameter." Karlas[9] has calculated that the error (about 2 per cent) between actual measurements and measurements on roentgenograms is least for this measurement in comparison with other measurements of "length." A perpendicular dropped from this line to the deepest portion of the pituitary fossa was used for measurement of the depth (D). The areas were tabulated with respect to age and again with respect to stature for males and females separately, and means of area for each age and height were determined. In addition, the fifth and ninety-fifth percentiles for each age and height were determined from the rough cumulative frequency curves by interpolation. Curves were "smoothed" by using a two point moving average. Using mean figures for area versus age, curves of annual increments were constructed.

In order to compare area and length-depth measurements, a table was constructed listing the mean area actually observed for the various combinations of length and depth (Tables III and IV).

RESULTS AND DISCUSSION

The mean areas of the pituitary fossa as measured in lateral roentgenograms of the skull from three months to eighteen years are shown with reference to age in Figure 3 and Tables I and II, and with reference to stature in Figure 4. The area-age curves

TABLE III

MEAN AREA OF PITUITARY FOSSA FOR GIVEN COMBINATIONS OF LENGTH AND DEPTH (BOYS)

	Depth in mm.							
	3	4	5	6	7	8	9	10
5	14.5 (4)	15.0 (3)	13.0 (1)	—	—	—	—	—
6	14.1 (15)	18 (25)	19.0 (7)	—	—	—	—	—
7	17.8 (12)	20.2 (49)	25.5 (28)	35.7 (15)	36 (5)	61 (4)	—	—
8	17.2 (6)	22.3 (41)	30.0 (38)	36.8 (23)	47.4 (22)	55.9 (14)	61.0 (1)	—
9	13.0 (1)	27.3 (22)	34.2 (62)	42.0 (77)	51.4 (75)	60.2 (50)	69.9 (14)	—
10	— —	31.7 (10)	38.1 (66)	46.7 (136)	55.8 (157)	65.0 (104)	74.8 (30)	87.5 (6)
11	— —	29.0 (1)	41.9 (33)	51.7 (98)	60.9 (189)	69.9 (133)	81.9 (42)	85.3 (9)
12	— —	45.0 (1)	47.0 (11)	57.6 (38)	64.3 (91)	72.9 (96)	81.3 (36)	92.3 (7)
13	— —	— —	43.9 (7)	55.2 (20)	69.7 (50)	78.1 (57)	87.3 (25)	95.0 (6)
14	— —	— —	61.0 (1)	66.8 (6)	73.6 (14)	81.0 (23)	87.6 (12)	97.0 (2)
15	— —	— —	— —	58.0 (1)	71.3 (4)	90.6 (11)	103.3 (6)	97.0 (1)
16	— —	— —	— —	— —	84.0 (2)	90.0 (1)	96.7 (3)	— —

Values in parentheses indicate the number of observations.

show a rapid increase in area during the first year and then a gradual deceleration in growth rate. The area-stature curves, on the other hand, suggest a relatively straight linear progression. This is probably more than an expression of the fact that an older child tends to be taller than a younger one. It suggests a real relationship between body size and pituitary fossa size which becomes more important when pathologic conditions are considered. Whether age or stature is considered, the pituitary fossa of males tends to be larger than that of females, from about one year of age until about thirteen years, when the pre-adolescent acceleration of growth in females which began two years earlier carries the females to, and subsequently beyond, the males.

Construction of curves of yearly increments of increase in pituitary fossa area (Fig. 5 and 6) shows somewhat more clearly the acceleration which occurs between the ages of eleven and fifteen years in the female and produces a significant change in

TABLE IV

MEAN AREA OF PITUITARY FOSSA FOR GIVEN COMBINATION OF LENGTH AND DEPTH (GIRLS)

	Depth in mm.							
	3	4	5	6	7	8	9	10
5	14.4 (5)	16.0 (4)	22.7 (3)	42.0 (1)	43.2 (6)	39.0 (1)	—	—
6	17.4 (9)	22.0 (40)	28.2 (16)	39.1 (12)	41.9 (12)	51.1 (7)	55.0 (1)	—
7	19.8 (11)	24.7 (41)	30.5 (43)	40.4 (57)	46.8 (57)	56.6 (27)	81.7 (3)	89.0 (2)
8	21.0 (4)	28.0 (45)	35.6 (60)	43.1 (81)	52.5 (104)	61.0 (60)	74.8 (8)	—
9	— —	32.0 (16)	41.0 (64)	47.9 (86)	55.2 (52)	66.7 (75)	75.7 (32)	84.9 (10)
10	— —	37.5 (8)	42.7 (53)	55.9 (80)	59.1 (115)	69.4 (121)	80.6 (29)	86.2 (10)
11	— —	— —	49.2 (18)	60.3 (21)	68.3 (76)	78.6 (74)	85.7 (39)	92.7 (3)
12	— —	— —	52.0 (1)	65.8 (13)	73.2 (24)	81.4 (33)	88.4 (23)	96.2 (6)
13	— —	— —	— —	65.4 (7)	78.6 (3)	85.4 (9)	93.8 (8)	— —
14	— —	— —	— —	— —	— —	— —	— —	— —
15	— —	— —	— —	— —	— —	— —	— —	— —
16	— —	— —	— —	— —	— —	— —	— —	— —

Values in parentheses indicate the number of observations.

pituitary fossa size. In the males, the acceleration occurs about two to three years later than in the females, is less pronounced, but may persist longer. During late adolescence this sustained growth acceleration in the male results in an approximate equalization in area in the sexes.

These observations differ in some respects from those of Francis,[5] who found a sex difference with females in advance of males up to eighteen years. However, he was measuring length; the reversal when area is considered may be an expression of differences in shape of the pituitary fossa. Our tables relating area to depth and length (Tables III and IV), however, would suggest that linear dimensions in our series correspond in sex differences to the area. The pre-adolescent spurt of growth in females was also noted by Francis who cited Rasmussen to the effect that females have larger pituitary glands during the 'teens than do males because of accelerated growth of the anterior lobe. This

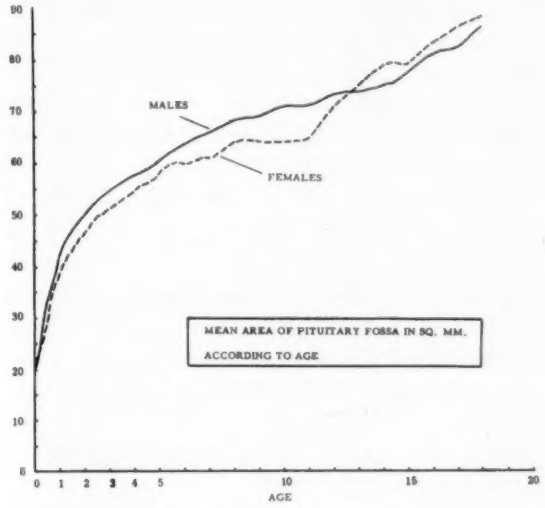


Fig. 3. Note pre-adolescent spurt of females.

growth pattern for the pituitary fossa (and presumably for the pituitary gland) is striking in its similarity to the general somatic growth pattern, and differs significantly from the neural pattern. At first consideration, one might anticipate a neural pattern for this structure which is derived in part from neural tissue and maintains physiologic and anatomic connections with the brain. Consideration of the functional activity of the pituitary gland, particularly its anterior lobe, removes any inconsistencies or conflict between the expected and the observed.

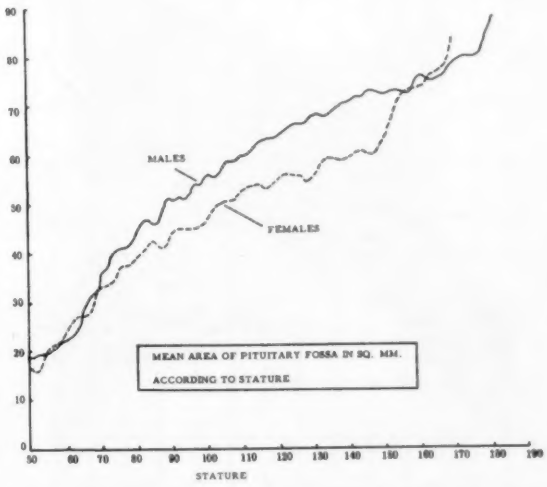


Fig. 4. The males and females maintain similar relationships as in Figure 3, but the general trend is more of a straight line.

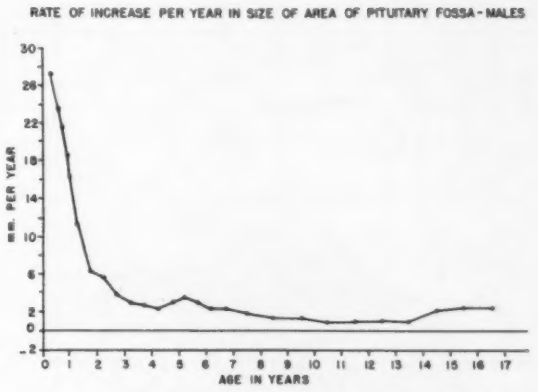


Fig. 5. The rate of increase in males falls rapidly in the first two years, shows a slight sustained increase beginning at about thirteen and one-half years.

Francis[5] and others before him[6,13] could find no relationship between pituitary fossa size (linear measurements) and other somatic measurements. Hare, *et al.*[8] recognized a relationship between stature and pituitary fossa size (area) using "height-age" as an indicator of area. This study too suggests that height (*i.e.*, size) may be a better standard for evaluation of pituitary fossa area than age. There is more of a straight line relationship between area and height than between area and age. It is possible that aberrations from the normal

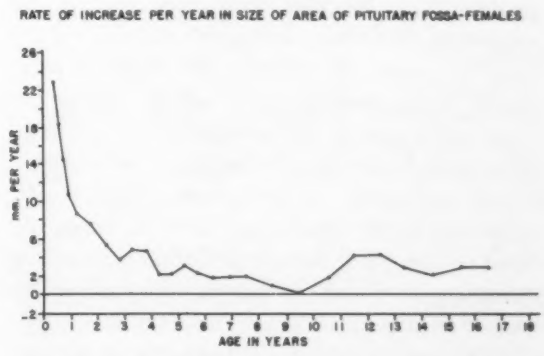


Fig. 6. The pre-adolescent spurt in girls begins two and one-half to three years earlier than in boys, is more pronounced, and begins to fall off about the time the boys begin their spurt. This is characteristic of somatic growth and differs from the pattern for neural growth.

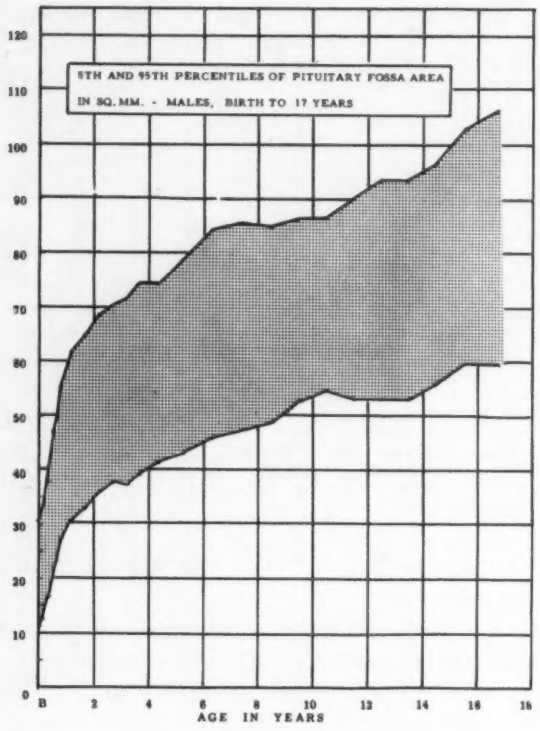


FIG. 7

may be recognized earlier and be more definite when the stature curve is used rather than the age curve. This is particularly true in those conditions in which stature is affected, *e.g.*, hypothyroidism.

The problem of what to measure is much greater than how to measure when one considers the pituitary fossa roentgenographically. As this study progressed, we began to think of it in terms of an accurate accumulation of inaccurate data. Variations in the configuration of the pituitary fossa produced by bulbous posterior clinoid processes, by prominent middle clinoid processes, and even by pneumatization of the sphenoid bone which appeared to make the floor of the pituitary fossa bulge upward in comparison with roentgenograms taken earlier in life all indicate the extreme range of variation in pituitary fossa size in normal children. Nevertheless, it is believed that the material presented does provide a means of evaluating pituitary fossae within the wide range of normal variation. The average radiologist would not have available a compensating polar planimeter to measure the area of the pituitary fossa. However, it is quite simple for him to measure the length and depth as outlined. By referring to the table for the appropriate sex, he can then note the mean area observed for that particular combination of length and depth. This mean figure is located on the graph (Fig. 7, 8, 9 or 10), and its position indicates the position of the pituitary fossa with respect to pituitary fossae from a group of normal children of the same age and the same height. A value for the area obtained from Table III or IV, which lies outside of the fifth and ninety-fifth percentiles would have real significance with respect to indicating a deviation from the normal.

The relationship of the size of the pituitary fossa in pathologic states will be the subject of a subsequent publication. Suffice it to say that hypothyroid children who have had inadequate treatment or who have had no treatment for years before be-

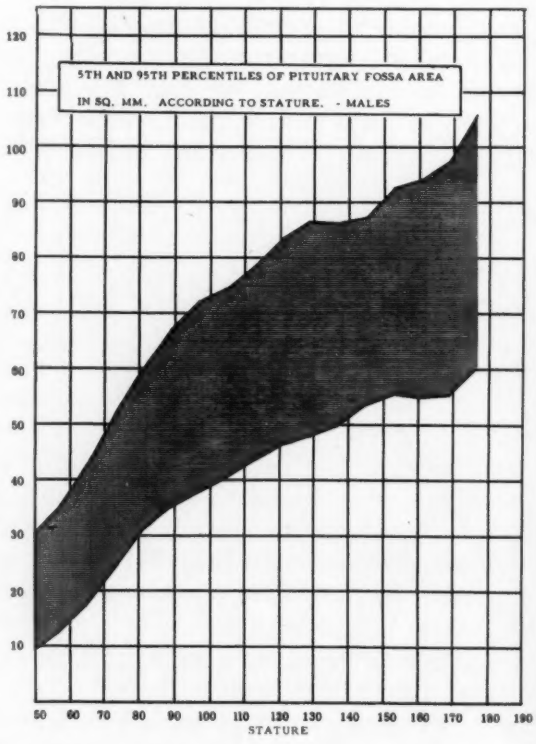


FIG. 8

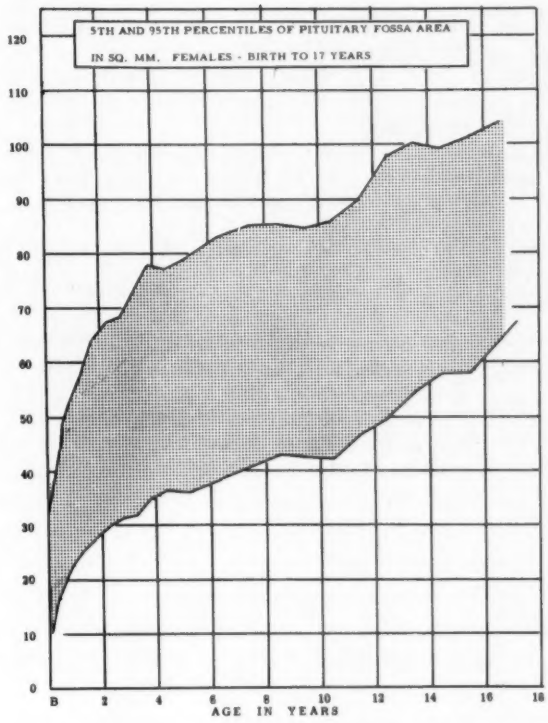


FIG. 9

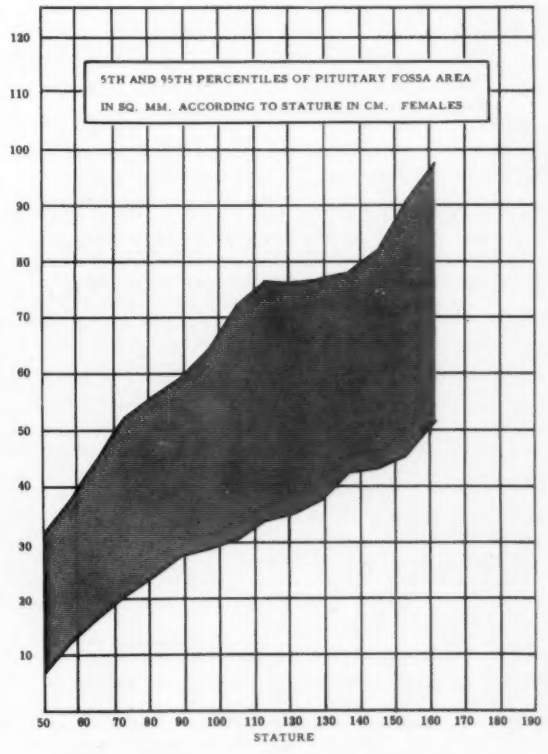


FIG. 10

ing recognized have generally shown pituitary fossae which fall outside of the range of normal for age, and even more so when the area is compared with respect to stature.

SUMMARY

Measurements of the area of the pituitary fossa as seen in lateral roentgenograms of the skull, were made planimetrically on 2,137 films from 168 boys, and on 1,899 films from 152 girls between the ages of one month and eighteen years. The children were participants in the longitudinal normative growth study of the Fels Research Institute, and their roentgenograms had been made serially in relation to birthday anniversaries. Measurements of "length" and "depth" of the pituitary fossa were also made.

Graphs have been prepared which define the range of normal variation (fifth and ninety-fifth percentiles) of the pituitary fossa area with respect to age and to stature respectively. Tables have been constructed to indicate the mean area associated with various combinations of "length" and "depth." From the standpoint of clinical application, these tables and graphs provide a technique for evaluation of pituitary fossa "size" based on a sample of adequate size and described in terms of range of normal rather than central tendency.

The Children's Hospital
Elland and Bethesda Avenues
Cincinnati 29, Ohio

The author is indebted for technical assistance to Janet Smart, Mary Argenteanu and Jennifer Young; and to Dr. Stanley Garn for advice and criticism.

REFERENCES

1. CAFFEY, J. Pediatric X-Ray Diagnosis, Third edition. Year Book Publishers, Inc., Chicago Ill., 1956, p. 115.
2. CAMP, J. D. Normal and pathologic anatomy of sella turcica as reviewed by roentgenograms. AM. J. ROENTGENOL. & RAD. THERAPY, 1924, *12*, 143–156.
3. ENFIELD, C. D. Normal sella. *J.A.M.A.*, 1922, *79*, 934–935.

4. FISCHGOLD, H., and METZGER, J. Examen de la loge hypophysaire normale; techniques radiographiques classifiques et récentes. *Presse méd.* (*Atlas radio. clin.*), 1953, *61*, 1–4.
5. FRANCIS, C. C. Growth of human pituitary fossa. *Human Biol.*, 1948, *20*, 1–20.
6. GORDON, M. B., and BELL, L. A. L. Roentgenographic study of sella turcica in normal children. *New York State J. Med.*, 1922, *22*, 54–59.
7. HAAS, L. Erfahrungen auf dem Gebiete der radiologischen Selladiagnostik. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1925, *33*, 419–422; 469–494.
8. HARE, H. F., SILVEUS, E., and SMEDAL, M. I. Roentgenologic diagnosis of pituitary tumors. *Radiology*, 1949, *52*, 193–198.
9. KARLAS, G. A. Morphological observations on superior surface of body of sphenoid bone in human adults (Inaugural Dissertation). Finland, Univ. of Helsingfors, 1948.
10. LE COULM, P. Étude radiologique de la sella turcique normale chez les enfants. Thesis, 1923, Paris.
11. PANCOAST, H. K., PENDERGRASS, E. P., and SCHAEFFER, J. P. The Head and Neck in Roentgen Diagnosis. Charles C Thomas, Publisher, Springfield, Ill., 1940, p. 591.
12. DE QUERVAIN, F., and WEGELIN, C. Der endemische Kretinismus. J. Springer, Berlin, 1936.
13. ROYSTER, L. T., and RODMAN, N. F. Size of sella turcica in relation to body measurements. *Trans. Am. Pediat. Soc.*, 1922, *34*, 246–266.
14. UNTERBERG, A. Sellamessung und Sellaformbestimmung bei Kindern in Alter bis zu 14 Jahren. *Mtschr. Kinderh.*, 1956, *104*, 46–50.

Vol. 78, No. 3

THE EFFECT OF PROLONGED NUTRITIVE FAILURE ON EPIPHYSEAL FUSION IN THE HUMAN HAND SKELETON*

By SAMUEL DREIZEN, D.D.S.,† RICHARD M. SNODGRASSE, PH.D.,‡ HAMILTON WEBB-PEPLOE,§ *and* TOM D. SPIES, M.D.‖

DOES protracted nutritive failure* during the growth period exert a detectable effect on human skeletal development? Are the manifestations reversible and how can correction be accomplished most expediently and most efficiently? In fifteen years of continuous study at the Nutrition Clinic of the Hillman Hospital, Birmingham, Alabama, it has been shown that children with long-standing nutritive failure have a slow rate of skeletal maturation,[4,14] a considerable degree of asymmetrical development in the hand skeleton,[9] a high frequency of anomalous bone centers in this area[10,11] and a pronounced retention of radiopaque transverse lines in the distal end of the shaft of the radius.[3] The stigmata in the skeleton respond in varying degrees to dietary supplements of reconstituted milk solids, provided the amount given is sufficient to overcome the accumulated nutritional deficiencies.[4,14] These studies have now been extended to determine the influence of chronic nutritive deprivation on epiphyseal fusion, the last stage of skeletal maturation.

* "The term 'nutritive failure' perhaps means different things to different physicians. It is used in our clinic to describe a variable clinical picture and does not have a specific physiologic connotation. It does not indicate why the nutrition has failed but simply that it has failed.

"Our work has convinced us that many times the physician cannot determine at once the physiologic basis of the nutritional insufficiency, and by the use of this term he can describe briefly the clinical picture without knowing the precise causation. The term has become so commonly entrenched in our clinical usage that it does not seem wise for us to restrict it or to change it.

"For the sake of clarity, the various disturbances and mechanisms which create a picture of nutritive failure we often describe separately. We can see pellagrous dermatitis or glossitis, beriberi neuritis or beriberi heart disease, scorbutic hemorrhages or gingivitis, cheilosis or the ocular symptoms of riboflavin deficiency as present symptoms arising as a response of the body to a long-continued deprivation of certain nutrients in food. Hence, nutritive failure is a more inclusive term than pellagra, beriberi, scurvy or riboflavin deficiency in that it connotes varying degrees of mixed deficiencies operating simultaneously."[13]

MATERIALS AND METHODS

Subjects for study were selected on the basis of the following criteria: (a) chronological age—16 to 18 years; (b) ethnic background—white, of British extraction; (c) geographic origin—native of Birmingham area; (d) health—absence of overt hormonal imbalance or debilitating disease other than nutritional in causation; (e) nutritional status—with or without a history and/or evidence of nutritive failure as determined by methods described in detail in a previous publication.[12] Two hundred and fifty-one members in the growth series of the Nutrition Clinic met each of these criteria; 118 (54 boys and 64 girls) with nutritive failure and 133 (53 boys and 80 girls) without nutritive failure. The chronological age distribution is shown in Table 1.

The fusion status of the phalanges, metacarpals, distal radius and ulna was determined by inspection of dorso-volar roentgenograms of the left hand of each of the 251 subjects. Fusion status was graded arbitrarily according to the following classification: 0 = no fusion; 1 = beginning fusion; 2 = fusion half complete; 3 = fusion complete, entire line of fusion visible; 4 = line of fusion obliterated.

Examples of each grade as seen in the distal end of the radius are presented in Figure 1. A half point scale was adopted

* Northwestern University studies in nutrition at the Jefferson-Hillman Hospital, Birmingham, Alabama. From the Department of Nutrition and Metabolism, Northwestern University.

These studies were supported by grants from Swift and Company and the Benjamin and Roberta Russell Educational and Charitable Foundations, Inc.

† Assistant Professor of Nutrition and Metabolism, Northwestern University Medical School.

‡ Professor of Anatomy, Temple University, School of Dentistry.

§ Research Technician, Nutrition Clinic, Hillman Hospital.

‖ Professor of Nutrition and Metabolism, Northwestern University Medical School.

FIG. 1. Classification of epiphyseal fusion in radius: (*A*) Grade 0; (*B*) Grade 1; (*C*) Grade 2; (*D*) Grade 3; (*E*) Grade 4.

for those instances in which the degree of fusion was intermediate between two grades.

The skeletal age of each hand was assessed by the Todd inspectional technique[15] using the Greulich-Pyle atlas[6] as the standard of reference. Height and weight obtained for each subject at the time of taking the hand roentgenogram were plotted on Wetzel grids.[16] All data were then subjected to statistical analysis.

OBSERVATIONS

The degree of fusion of epiphysis with shaft in each of the 21 bones in the skeletal area under consideration is contained in Tables II and III. Irrespective of nutritional status, fusion was more advanced in the girls than in the boys in each group. Absence of any roentgenographic indication of epiphyseal closure (Grade 0) ranged from 0 per cent (distal radius) to 3.1 per cent (distal ulna) in the girls and from 7.4 per

Table I

CHRONOLOGICAL AGE DISTRIBUTION OF 118 CHILDREN WITH NUTRITIVE FAILURE AND 133 CHILDREN WITHOUT NUTRITIVE FAILURE

Chronological Age (Years-Months)	Series with Nutritive Failure			Control Series		
	Boys	Girls	Total	Boys	Girls	Total
16-0 to 16-3	7	9	16	5	8	13
16-3 to 16-6	8	9	17	4	9	13
16-6 to 16-9	9	7	16	8	7	15
16-9 to 17-0	7	9	16	7	15	22
17-0 to 17-3	7	4	11	5	11	16
17-3 to 17-6	4	7	11	7	12	19
17-6 to 17-9	5	9	14	9	6	15
17-9 to 18-0	7	10	17	8	12	20
Total	54	64	118	53	80	133

cent (distal phalanx 1) to 55.5 per cent (distal ulna) in the boys with nutritive failure. In contrast, no bone in the entire control series had a fusion grade of 0. Evidence of beginning to incomplete epiphyseal fusion (Grades 1 through 2.5 collectively) ranged from 1.6 per cent (distal phalanges 1, II, III, IV) to 36.0 per cent (distal ulna) in girls and from 18.6 per cent (distal phalanx 1) to 48.2 per cent (metacarpal III) in boys in the group with nutritive failure. Fusion grades of 1 through 2.5 were found only in boys in the control series. These were seen mainly in the distal radius and ulna, the incidence in the other bones being negligible. In general, the sequence of closure was similar in each group starting in the distal phalanges and proceeding in order through the metacarpals, middle and proximal phalanges, distal end of the ulna and distal end of the radius. In each group and for each sex, however, the thumb metacarpal lagged far behind the other members of this segment in fusion grade.

Eighty (100.0 per cent) girls and 30 (56.6 per cent) boys in the control group had fusion grades of 3 or more for all metacarpals, phalanges, and distal ulna and radius (Tables II and III). In the group with nutritive failure, the corresponding numbers were 36 (56.3 per cent) girls and 3 (5.6 per cent) boys. Application of the chi square test[8] yielded chi values of 5.73 and 6.60 for the boys and girls, respectively. These figures are highly significant statistically and denote that the observed disparities between groups are not ascribable to chance. Twenty (37.0 per cent) boys and 1 (1.6 per cent) girl in the group with nutritive failure had fusion grades of 2.5 or less for each of the 21 bones examined. Every member of the control group had a fusion grade of 3 or higher for at least several of these bones. The difference between groups was significant for the boys (chi $=4.94$) and not significant for the girls (chi $=1.12$).

Illustrative of the extent to which dissimilarities in fusion status accompanied differences in nutritional status during the growth period are the roentgenograms shown in Figure 2. Each boy was 18 years old, the actual difference in age being 7 days. In the boy with chronic nutritive failure, who has been followed in the Nutrition Clinic since the age of 6, all epiphyses are noticeably open, except for distal phalanx III, in sharp contrast to the complete closure which characterizes the hand of the boy from the control group.

The association between skeletal maturational status and presence of complete closure (Grades 3 through 4) in all 21 epiphyses is presented in Table IV. Eleven (9.3 per cent) subjects with nutritive fail-

TABLE II

COMPARISON OF FUSION STATUS IN PHALANGES, METACARPALS AND DISTAL RADIUS AND ULNA OF 54 BOYS WITH NUTRITIVE FAILURE AND 53 BOYS WITHOUT NUTRITIVE FAILURE

Bone	Grade of Epiphyseal Fusion															
	0		1		1.5		2		2.5		3		3.5		4	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Boys with Nutritive Failure																
Radius	22	40.7	9	15.7	10	18.5	5	9.3	3	5.6	3	5.6	0	0.0	2	3.7
Ulna	30	55.5	14	25.9	2	3.7	5	9.3	0	0.0	1	1.9	0	0.0	2	3.7
Metacarpal I	12	22.2	4	7.4	2	3.7	2	3.7	3	5.6	20	37.0	9	15.7	2	3.7
Metacarpal II	9	15.7	7	13.0	3	5.6	4	7.4	10	18.5	8	14.8	1	1.9	12	22.2
Metacarpal III	9	15.7	10	18.5	0	0.0	3	5.6	13	24.1	4	7.4	3	5.6	12	22.2
Metacarpal IV	14	25.9	7	13.0	0	0.0	2	3.7	13	24.1	2	3.7	1	1.9	15	27.8
Metacarpal V	14	25.9	7	13.0	1	1.9	6	11.1	9	15.7	2	3.7	1	1.9	14	25.9
Prox. Phalanx I	12	22.2	7	13.0	3	5.6	2	3.7	6	11.1	12	22.2	6	11.1	6	11.1
Prox. Phalanx II	13	24.1	6	11.1	4	7.4	3	5.6	3	5.6	11	20.4	9	15.7	5	9.3
Prox. Phalanx III	8	14.8	10	18.5	4	7.4	3	5.6	5	9.3	9	15.7	9	15.7	6	11.1
Prox. Phalanx IV	11	20.4	7	13.0	4	7.4	2	3.7	8	14.8	6	11.1	16	29.6	0	0.0
Prox. Phalanx V	15	27.8	3	5.6	1	1.9	5	9.3	6	11.1	8	14.8	12	22.2	4	7.4
Middle Phalanx II	12	22.2	6	11.1	1	1.9	5	9.3	7	13.0	5	9.3	11	20.4	7	13.0
Middle Phalanx III	13	24.1	4	7.4	3	5.6	6	11.1	8	14.8	7	13.0	11	20.4	2	3.7
Middle Phalanx IV	14	25.9	3	5.6	4	7.4	5	9.3	9	15.7	4	7.4	12	22.2	3	5.6
Middle Phalanx V	13	24.1	6	11.1	2	3.7	5	9.3	5	9.3	8	14.8	9	15.7	6	11.1
Distal Phalanx I	4	7.4	1	1.9	1	1.9	4	7.4	4	7.4	19	35.2	10	18.5	11	20.4
Distal Phalanx II	7	13.0	6	11.1	1	1.9	1	1.9	2	3.7	11	20.4	18	33.3	8	14.8
Distal Phalanx III	9	15.7	3	5.6	0	0.0	3	5.6	5	9.3	14	25.9	10	18.5	10	18.5
Distal Phalanx IV	10	18.5	4	7.4	0	0.0	3	5.6	3	5.6	14	25.9	14	25.9	6	11.1
Distal Phalanx V	13	24.1	2	3.7	3	5.6	0	0.0	2	3.7	12	22.2	16	29.6	6	11.1
Boys without Nutritive Failure																
Radius	0	0.0	0	0.0	0	0.0	12	22.6	4	7.5	15	28.3	14	26.4	8	15.1
Ulna	0	0.0	1	1.9	2	3.8	8	15.1	7	13.2	11	20.8	9	17.0	15	28.3
Metacarpal I	0	0.0	0	0.0	0	0.0	1	1.9	0	0.0	7	13.2	36	67.9	9	17.0
Metacarpal II	0	0.0	0	0.0	0	0.0	1	1.9	1	1.9	2	3.8	9	17.0	40	75.5
Metacarpal III	0	0.0	0	0.0	0	0.0	1	1.9	1	1.9	2	3.8	4	7.5	45	84.9
Metacarpal IV	0	0.0	0	0.0	0	0.0	2	3.8	0	0.0	2	3.8	4	7.5	45	84.9
Metacarpal V	0	0.0	0	0.0	0	0.0	2	3.8	0	0.0	1	1.9	6	11.3	44	83.0
Prox. Phalanx I	0	0.0	0	0.0	0	0.0	1	1.9	0	0.0	1	1.9	12	22.6	39	73.6
Prox. Phalanx II	0	0.0	0	0.0	1	1.9	0	0.0	0	0.0	1	1.9	20	37.7	31	58.5
Prox. Phalanx III	0	0.0	0	0.0	1	1.9	0	0.0	0	0.0	4	7.5	26	49.1	22	41.5
Prox. Phalanx IV	0	0.0	0	0.0	1	1.9	0	0.0	0	0.0	3	5.7	29	54.7	20	37.7
Prox. Phalanx V	0	0.0	0	0.0	1	1.9	0	0.0	0	0.0	2	3.8	28	52.8	22	41.5
Middle Phalanx II	0	0.0	0	0.0	0	0.0	0	0.0	1	1.9	0	0.0	17	32.1	35	66.0
Middle Phalanx III	0	0.0	0	0.0	0	0.0	1	1.9	0	0.0	1	1.9	25	47.2	26	49.1
Middle Phalanx IV	0	0.0	0	0.0	0	0.0	1	1.9	0	0.0	2	3.8	20	37.7	30	56.4
Middle Phalanx V	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	10	18.9	43	86.8
Distal Phalanx I	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.9	16	30.2	36	67.9
Distal Phalanx II	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.9	17	32.1	35	66.0
Distal Phalanx III	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	27	50.9	26	49.1
Distal Phalanx IV	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	26	49.1	27	50.9
Distal Phalanx V	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.9	21	39.6	31	58.5

Table III

COMPARISON OF FUSION STATUS IN PHALANGES, METACARPALS AND DISTAL RADIUS AND ULNA OF 64 GIRLS WITH NUTRITIVE FAILURE AND 80 GIRLS WITHOUT NUTRITIVE FAILURE

Bone	Grade of Epiphyseal Fusion															
	0		1		1.5		2		2.5		3		3.5		4	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Girls with Nutritive Failure																
Radius	0	0.0	2	3.1	3	4.7	6	9.4	9	14.1	11	17.2	22	34.4	11	17.2
Ulna	2	3.1	4	6.3	3	4.7	7	10.9	9	14.1	18	28.1	12	18.8	9	14.1
Metacarpal I	1	1.6	0	0.0	0	0.0	0	0.0	2	3.1	6	9.4	45	70.3	10	15.6
Metacarpal II	0	0.0	1	1.6	0	0.0	0	0.0	1	1.6	4	6.3	4	6.3	54	84.4
Metacarpal III	0	0.0	1	1.6	0	0.0	0	0.0	0	0.0	4	6.3	4	6.3	55	85.9
Metacarpal IV	0	0.0	1	1.6	0	0.0	0	0.0	1	1.6	4	6.3	3	4.7	55	85.9
Metacarpal V	1	1.6	0	0.0	1	1.6	1	1.6	2	3.1	1	1.6	5	7.8	53	82.8
Prox. Phalanx I	1	1.6	0	0.0	2	3.1	1	1.6	1	1.6	2	3.1	30	46.9	27	42.2
Prox. Phalanx II	1	1.6	0	0.0	0	0.0	2	3.1	2	3.1	2	3.1	32	50.0	25	39.1
Prox. Phalanx III	1	1.6	0	0.0	0	0.0	2	3.1	2	3.1	2	3.1	44	68.8	13	20.3
Prox. Phalanx IV	1	1.6	0	0.0	1	1.6	1	1.6	3	4.7	0	0.0	40	62.5	18	28.1
Prox. Phalanx V	1	1.6	0	0.0	0	0.0	2	3.1	1	1.6	4	6.3	40	62.5	16	25.0
Middle Phalanx II	1	1.6	0	0.0	1	1.6	3	4.7	1	1.6	1	1.6	23	35.9	34	51.6
Middle Phalanx III	1	1.6	0	0.0	1	1.6	2	3.1	2	3.1	2	3.1	35	54.7	21	32.8
Middle Phalanx IV	1	1.6	0	0.0	2	3.1	2	3.1	1	1.6	2	3.1	32	50.0	24	37.5
Middle Phalanx V	1	1.6	1	1.6	1	1.6	1	1.6	1	1.6	3	4.7	20	31.3	36	56.3
Distal Phalanx I	1	1.6	0	0.0	0	0.0	0	0.0	1	1.6	4	6.3	35	54.7	23	35.9
Distal Phalanx II	1	1.6	0	0.0	0	0.0	0	0.0	1	1.6	5	7.8	35	54.7	22	34.4
Distal Phalanx III	1	1.6	0	0.0	0	0.0	0	0.0	1	1.6	3	4.7	42	65.6	17	26.5
Distal Phalanx IV	1	1.6	0	0.0	0	0.0	0	0.0	1	1.6	5	7.8	36	56.3	21	32.8
Distal Phalanx V	1	1.6	0	0.0	0	0.0	0	0.0	2	3.1	2	3.1	43	67.2	16	25.0
Girls without Nutritive Failure																
Radius	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	5	6.3	19	23.8	56	70.0
Ulna	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	2.5	9	11.3	69	86.3
Metacarpal I	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	3	3.8	67	83.8	10	12.5
Metacarpal II	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	4	5.0	76	95.0
Metacarpal III	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	4	5.0	76	95.0
Metacarpal IV	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	4	5.0	76	95.0
Metacarpal V	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	4	5.0	76	95.0
Prox. Phalanx I	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	2.5	40	50.0	38	47.5
Prox. Phalanx II	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	39	48.8	41	51.3
Prox. Phalanx III	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.3	53	66.3	26	31.5
Prox. Phalanx IV	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.3	52	65.0	27	33.8
Prox. Phalanx V	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	51	63.8	29	36.3
Middle Phalanx II	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	32	40.0	48	60.0
Middle Phalanx III	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.3	36	45.0	43	53.8
Middle Phalanx IV	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.3	30	37.5	49	61.3
Middle Phalanx V	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	20	25.0	60	75.0
Distal Phalanx I	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	39	48.8	41	51.3
Distal Phalanx II	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.3	38	47.5	41	51.3
Distal Phalanx III	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.3	34	41.5	45	56.3
Distal Phalanx IV	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.3	36	45.0	43	53.8
Distal Phalanx V	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.3	43	53.8	36	45.0

FIG. 2. (*A* and *B*) Comparison of fusion status in eighteen year old boys with nutritive failure (*A*) and without nutritive failure (*B*).

ure and 59 (44.3 per cent) without nutritive failure had skeletal ages which equalled or surpassed chronological age. Of these, 81.9 per cent in the group with nutritive failure and 94.9 per cent in the control group showed complete fusion of all epiphyses. The corresponding values for subjects with a chronological age in excess of skeletal age

TABLE IV

COMPARISON OF FUSION STATUS WITH SKELETAL MATURATIONAL STATUS IN 118 CHILDREN WITH NUTRITIVE FAILURE AND 133 CHILDREN WITHOUT NUTRITIVE FAILURE

Group	Skeletal Age > Chronological Age					Skeletal Age = Chronological Age					Skeletal Age < Chronological Age				
	No.	No. Fused	Per Cent Fused	No. Not Fused	Per Cent Not Fused	No.	No. Fused	Per Cent Fused	No. Not Fused	Per Cent Not Fused	No.	No. Fused	Per Cent Fused	No. Not Fused	Per Cent Not Fused
Nutritive Failure															
Boys	2	2	100.0	0	0.0	1	0	0.0	1	100.0	51	1	1.9	50	98.1
Girls	7	6	85.7	1	14.3	1	1	100.0	0	0.0	56	29	51.8	27	48.2
Total	9	8	88.9	1	11.1	2	1	50.0	1	50.0	107	30	28.0	77	72.0
Control															
Boys	20	18	90.0	2	10.0	5	4	80.0	1	20.0	28	8	28.6	20	71.4
Girls	28	28	100.0	0	0.0	6	6	100.0	0	0.0	46	46	100.0	0	0.0
Total	48	46	95.9	2	4.1	11	10	90.9	1	9.1	74	54	73.0	20	27.0

TABLE V

STATISTICAL EVALUATION OF DIFFERENCES BETWEEN 118 CHILDREN WITH NUTRITIVE FAILURE AND 133 CHILDREN WITHOUT NUTRITIVE FAILURE

Group	Weight (pounds)				Height (inches)				C.A.—S.A. Diff. (Months)				Fusion Status (hand)		
	Mean	σ	σ_D	Diff. / σ_D	Mean	σ	σ_D	Diff. / σ_D	Mean	σ	σ_D	Diff. / σ_D	Complete	Incomplete	Chi Value
Boys															
Nutritive Failure	126.2	17.2	4.74	6.46	67.4	2.18	0.449	3.78	−13.55	14.60	2.20	5.90	3	51	5.73
Control	156.8	29.8			69.1	2.45			− 0.49	3.84			30	23	
Difference	30.6				1.7				13.06						
Girls															
Nutritive Failure	111.7	14.1	2.47	3.52	63.5	2.05	0.332	1.78	−12.07	11.00	1.46	7.60	36	28	6.60
Control	121.4	15.4			64.1	2.08			− 0.63	4.44			80	0	
Difference	9.7				0.6				11.44						

were 28.0 per cent for the group with nutritive failure and 73.0 per cent for the control series.

In each group and for each sex, mean chronological age exceeded mean skeletal age. The mean differences were 13.55 months for boys with nutritive failure, 12.07 months for girls with nutritive failure, 0.49 month for boys in the control group and 0.63 month for girls in the control group. The standard errors of difference between means (σ_D) were 2.20 (boys) and 1.46 (girls). In each instance, the actual difference between means was more than 3 times the standard error of difference between means required for statistical significance.

Table v contains an evaluation of the disparities in height and weight between each series for both sexes. Mean differentials in favor of the control group amounted to 1.7 inches and 30.6 pounds for the boys and 0.6 inch and 9.7 pounds for the girls. Except for height in girls, all differences between the means were statistically significant.

The data derived from an analysis of the individual height and weight measurements by means of the Wetzel grid are shown in Tables v and vi. On the physique channel panel, which designates the direction of development, the distribution for the group with nutritive failure was 11.2 per cent in channels to the left of A_1, 47.7 per cent between A_1 and B_1, and 40.6 per cent in channels to the right of B_1. The respective

TABLE VI

WETZEL GRID PHYSIQUE CHANNEL POSITIONS OF 118 CHILDREN WITH NUTRITIVE FAILURE AND 133 CHILDREN WITHOUT NUTRITIVE FAILURE

Group	Per Cent in Each Channel															
	A_4	A_3A_4	A_3	A_2A_3	A_2	A_1A_2	A_1	A_1M	M	MB_1	B_1	B_1B_2	B_2	B_2B_3	B_3	B_3B_4	B_4
Nutritive Failure																	
Boys	0.0	0.0	5.7	0.0	1.9	0.0	5.7	1.9	17.0	5.7	17.0	3.8	13.2	3.8	15.1	3.8	5.7
Girls	1.6	0.0	1.6	1.6	7.8	1.6	12.5	1.6	20.3	3.1	10.9	4.7	21.9	0.0	3.1	1.6	6.3
Total	0.9	0.0	3.4	0.9	5.1	0.9	9.3	1.7	18.6	4.2	13.6	4.2	17.8	1.7	8.5	2.5	5.9
Control																	
Boys	22.6	0.0	7.5	1.9	7.5	0.0	7.5	0.0	9.4	1.9	18.8	5.7	9.4	1.9	1.9	3.8	0.0
Girls	5.0	2.5	8.8	0.0	8.8	2.5	16.3	3.8	17.5	1.3	18.8	2.5	6.3	3.8	2.5	0.0	0.0
Total	12.0	1.5	8.3	0.8	8.3	1.5	12.8	2.3	14.3	1.5	18.8	3.8	7.5	3.0	2.3	1.5	0.0

TABLE VII

WETZEL GRID AUXODROME POSITIONS OF 118 CHILDREN WITH NUTRITIVE FAILURE AND 133 CHILDREN WITHOUT NUTRITIVE FAILURE

Group	Per Cent in Each Auxodrome Panel										
	0–2	2	2–15	15	15–67	67	67–82	82	82–98	98	98–100
Nutritive Failure											
Boys	0.0	0.0	9.3	0.0	9.3	3.8	42.6	1.9	14.8	3.8	14.8
Girls	0.0	0.0	0.0	0.0	1.6	28.1	12.5	1.6	42.2	7.8	6.3
Total	0.0	0.0	4.2	0.0	5.1	16.9	26.2	1.7	29.7	5.9	10.1
Control											
Boys	20.8	1.9	17.0	0.0	18.8	15.1	17.0	0.0	9.4	0.0	0.0
Girls	0.0	0.0	1.3	8.8	11.3	28.8	12.5	2.5	31.3	2.5	1.3
Total	8.3	0.8	7.5	4.5	14.3	23.3	14.3	1.5	22.6	1.5	0.8

spread in the control groups was 32.4, 49.7 and 18.1 per cent. On the auxodrome panel, which depicts the speed of development, 30 (56.6 per cent) boys and 17 (21.3 per cent) girls in the control series were to the left of the 67 per cent standard auxodrome, 8 (15.1 per cent) boys and 23 (28.8 per cent) girls were directly on the 67 per cent auxodrome and 14 (26.4 per cent) boys and 40 (50.0 per cent) girls were to the right of the 67 per cent auxodrome. The corresponding numbers for the group with nutritive failure were: boys, 10 (18.5 per cent), 2 (3.8 per cent), and 42 (77.7 per cent); girls, 1 (1.6 per cent), 18 (26.1 per cent), and 45 (70.3 per cent). In neither group was the relationship between channel and auxodrome position and frequency of complete fusion (Grades 3 through 4) in all 21 bones of the hand statistically significant.

DISCUSSION

Ossification of the cartilage between epiphysis and shaft which denotes the terminal phase of skeletal maturation in the phalanges, metacarpals and distal radius and ulna is presumably under hormonal control. In the human hand, the time schedule for epiphyseal fusion varies with the sex and with the particular anatomic segment.[1,2,5,7] In health, the process is orderly and predictable as to time and site. In prolonged illness, severe acute starvation and hormonal dyscrasias involving the adrenal cortex, gonads, thyroid or anterior lobe of pituitary, the pattern may be profoundly altered. The distribution of epiphyseal union in the hands of the 16 to 18 year old subjects comprising the control group is in general accord with the fusion ages for each sex listed by Todd[15] and Greulich and Pyle.[6] The significant differences in prevalence of epiphyseal closure between the groups with and without nutritive failure indicate that chronic undernutrition retards bony union between epiphysis and diaphysis in the hand skeleton to a detectable degree.

The delay in epiphyseal fusion in the group with nutritive failure averaged slightly more than one year in each sex. Endocrine disturbances, non-nutritional chronic diseases and acute starvation were not precipitating factors in these cases. Hence, it may be inferred that protracted nutritive failure acts to prolong the growth period by interfering with the attainment of skeletal maturity in the usually allotted time. Whether the delayed fusion affords an opportunity for the complete correction of growth failure by dietary means is uncertain. Todd[15] holds that if inhibition of progress in skeletal maturation is sufficiently great during the preschool period as to be apparent, the chances of restoration during adolescence are very slight. This problem certainly bears investigation in light of

the tremendous advances which have been made in nutrition and endocrinology during the past 20 years.

Skeletal maturation must be distinguished from dimensional growth. The prevalence of epiphyseal fusion was not related to the Wetzel grid positions despite significant differences in mean weight (boys and girls) and mean height (boys) between the groups with and without nutritive failure. This denotes that over-all body size is not a determinant of skeletal maturity. Both maturation and dimensional increase apparently have their own controlling factors which are affected to a different degree by the same intensity of nutritive failure.

SUMMARY AND CONCLUSIONS

The gross roentgenographic manifestations of the successive stages of bony union between shaft and epiphysis, as shown in Figure 1, were converted into an arbitrarily devised scale of epiphyseal closure. This scale was used to evaluate fusion status in 21 bones in the hand and wrist of 251 ethnically comparable adolescents 16 through 18 years of age. Comparisons were made between subjects grouped on the basis of nutritional status and subgrouped on the basis of over-all body size. This study clearly shows that:

1. Prolonged nutritive failure during childhood and adolescence delays epiphyseal fusion in the long bones.

2. The delay in fusion is quantitatively similar in boys and girls despite the more rapid rate of skeletal maturation characteristic of girls.

3. In the absence of primary hormonal disease, epiphyseal fusion is not related to body size.

4. The findings support our hypothesis that undernutrition initiates biologic changes which often linger for long and indeterminate periods.

Tom D. Spies, M. D.
Nutrition Clinic
Hillman Hospital
Birmingham, Alabama

REFERENCES

1. Brailsford, J. F. The Radiology of Bones and Joints; An Introduction to the Study of Tumors and Other Diseases of Bone. Fifth Edition. Williams & Wilkins Company, Baltimore, 1953.
2. Camp, J. D., and Cilley, E. I. L. Diagrammatic chart showing time of appearance of various centers of ossification and period of union. Am. J. Roentgenol. & Rad. Therapy, 1931, *26*, 905.
3. Dreizen, S., Currie, C., Gilley, E. J., and Spies, T. D. Observations on association between nutritive failure, skeletal maturation rate and radiopaque transverse lines in distal end of radius in children. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1956, *76*, 482–487.
4. Dreizen, S., Snodgrasse, R. M., Parker, G. S., Currie, C., and Spies, T. D. Maturation of bone centers in hand and wrist of children with chronic nutritive failure; effect of dietary supplements of reconstituted milk solids. *A.M.A. Am. J. Dis. Child.*, 1954, *87*, 429–439.
5. Flecker, H. Time of appearance and fusion of ossification centers as observed by roentgenographic methods. Am. J. Roentgenol. & Rad. Therapy, 1942, *47*, 97–159.
6. Greulich, W. W., and Pyle, S. I. Radiographic Atlas of Skeletal Development of the Hand and Wrist. Stanford University Press, Stanford University, California, 1950.
7. Hodges, P. C. Epiphyseal chart. Am. J. Roentgenol. & Rad. Therapy, 1933, *30*, 809–810.
8. Pearl, R. Introduction to Medical Biometry and Statistics. Second edition. W. B. Saunders Company, Philadelphia, 1930.
9. Pyle, S. I., Mann, A. W., Dreizen, S., Kelly, H. J., Macy, I. G., and Spies, T. D. Substitute for skeletal age (Todd) for clinical use; red graph method. *J. Pediat.*, 1948, *32*, 125–136.
10. Snodgrasse, R. M., Dreizen, S., Currie, C., Parker, G. S., and Spies, T. D. Association between anomalous ossification centers in hand skeleton, nutritional status and rate of skeletal maturation in children five to fourteen years of age. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1955, *74*, 1037–1048.
11. Snodgrasse, R. M., Dreizen, S., Parker, G. S., and Spies, T. D. Serial sequential development of anomalous metacarpal and phalangeal ossification centers in human hand. *Growth*, 1955, *19*, 307.
12. Spies, T. D. Principles of diet in treatment of disease. *J.A.M.A.*, 1943, *122*, 497–502.

13. SPIES, T. D. Nutrition in rehabilitation. *M. Clin. North America*, 1945, *29*, 749–806.

14. SPIES, T. D., DREIZEN, S., SNODGRASSE, R. M., PARKER, G. S., and CURRIE, C. Skeletal maturational progress of children with chronic nutritive failure. *A.M.A. Am. J. Dis. Child.*, 1953, *85*, 1–12.

15. TODD, T. W., and others. Atlas of Skeletal Maturation. C. V. Mosby Company, St. Louis, 1937.

16. WETZEL, N. C. Physical fitness in terms of physique, development and basal metabolism. *J.A.M.A.*, 1941, *116*, 1187–1195.

Vol. 78, No. 3

PRIMARY PULMONARY HYPERTENSION IN BROTHERS*

By EUGENE F. VAN EPPS, M.D.
IOWA CITY, IOWA

PRIMARY pulmonary hypertension, or primary pulmonary vascular disease is now a distinct clinical entity, and since the introduction of cardiac catheterization, it is found so frequently that it no longer can be considered a rarity.[2,3,4,6,8,12–14,16,19,20,23,27,28] Therefore, radiologists must be alert and sensitive to alterations in the normal architecture of the pulmonary vascular tree not only on plain roentgenograms of the chest, but also when the pulmonary arteries are opacified by contrast substance. Obviously, the radiologist contributes a great deal when he excludes the causes of secondary pulmonary hypertension. These include the following: mitral stenosis, patent ductus arteriosus, ventricular septal defect, atrial septal defect, pulmonary fibrosis with or without pneumoconiosis or sarcoidosis, emphysema, kyphoscoliosis, miliary pulmonary carcinomatosis, cystic disease of the lungs and repeated pulmonary emboli.[2,5,9,10 11,15,16,17,18,22,24,25,26]

Primary pulmonary hypertension usually occurs in the age group between twenty and forty years. However, the reported cases range from twenty months[7] to seventy-four years.[21] Females are somewhat more prone to this disease than are males. Clinically the patients appear in good health, but complain of shortness of breath on exertion initially. This symptom may be present for only a few months, or may continue for several years. As the disease progresses there develops cough, weakness, easy fatigability, precordial pain simulating angina, exertional syncope due to acute right heart failure,[13,20] and rarely palpitation. Hemoptysis is an uncommon complaint, but has been reported. As the disease progresses further orthopnea, cyanosis with or without polycythemia and edema develop. Death, when it occurs, is characteristically quite sudden. On physical examination there is evidence of right ventricular enlargement and overactivity. The second pulmonary sound is accentuated. If any cardiac murmur is present, it is usually systolic in time, and found at the pulmonic area or at the apex. Occasionally a Graham Steell murmur of pulmonic incompetence is heard. Blood pressure is normal. The electrocardiographic findings are consistent with right ventricular hypertrophy.

The following two case reports emphasize the clinical and roentgenographic findings in children. These roentgenographic criteria apply equally well to adults with this disease.

REPORT OF CASES

CASE 1. R.W., male, aged six when first seen at State University of Iowa Hospitals, was born on September 28, 1946. Pregnancy and labor were normal. Weight at birth was 6 pounds 13 ounces. In November of 1950, when he was four years old, a murmur was heard following whooping cough, tonsillitis and pneumonia. The only complaint given by the mother was that the boy tired more easily than usual. He had no shortness of breath, but at high altitudes (Colorado) he would go to sleep. When he played hard, his lips would become pale and blue.

On June 25, 1952, he was first seen at University Hospitals. Aside from low normal weight and height standards, the positive physical findings were restricted to the heart. Whereas there was no cardiac enlargement, there was a Grade II harsh systolic murmur in the left second and third intercostal spaces, radiating into the axilla, neck and to the cardiac apex. There was no enlargement of the liver and no ascites. No cyanosis was detected.

Fluoroscopic and roentgenographic examination of the heart and lungs (Fig. 1) revealed I

* From Department of Radiology, College of Medicine, State University of Iowa, Iowa City, Iowa. Presented at the Fifty-sixth Annual Meeting of the American Roentgen Ray Society, Chicago, Illinois, September 20–23, 1955.

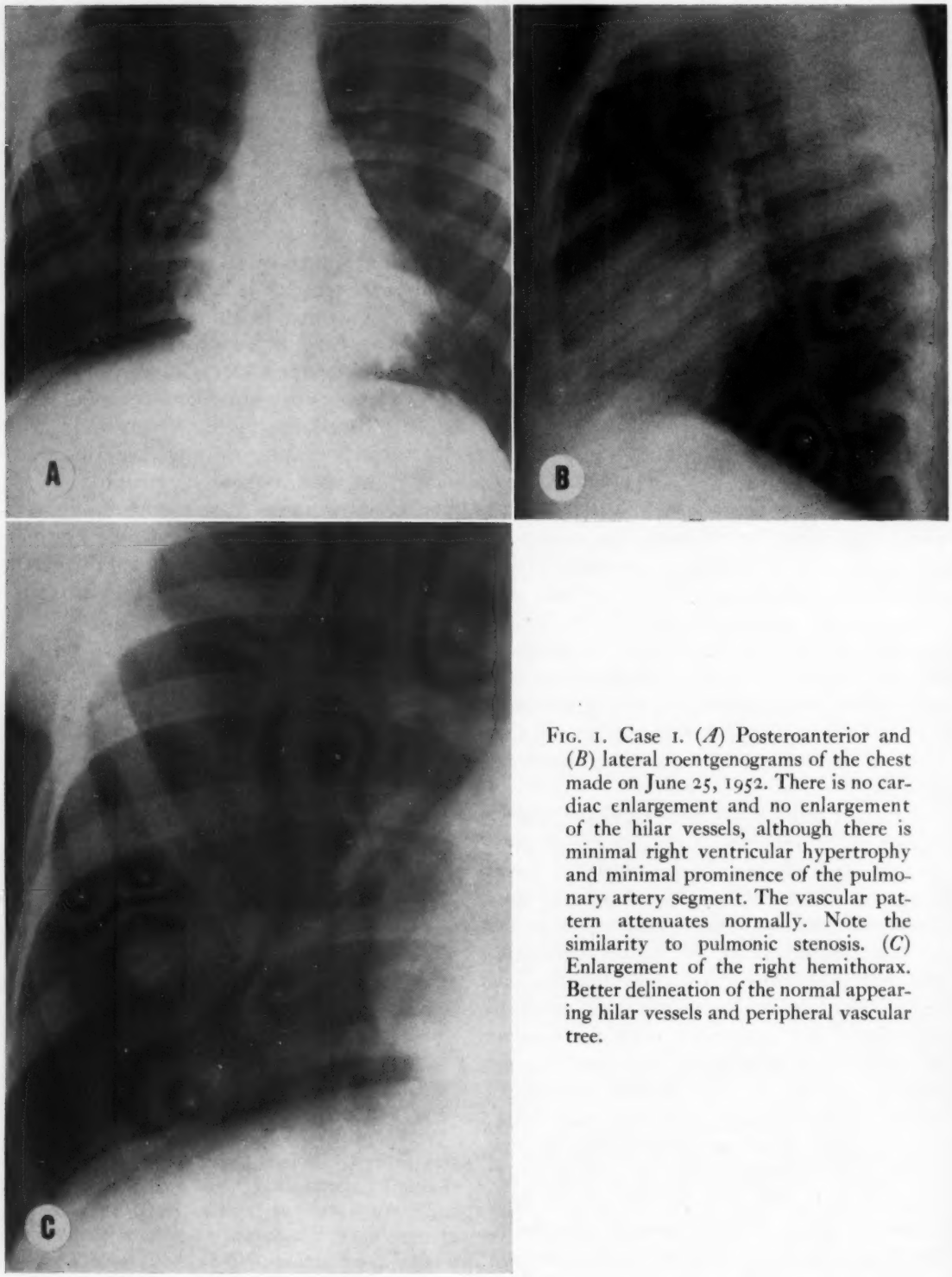


FIG. 1. Case 1. (*A*) Posteroanterior and (*B*) lateral roentgenograms of the chest made on June 25, 1952. There is no cardiac enlargement and no enlargement of the hilar vessels, although there is minimal right ventricular hypertrophy and minimal prominence of the pulmonary artery segment. The vascular pattern attenuates normally. Note the similarity to pulmonic stenosis. (*C*) Enlargement of the right hemithorax. Better delineation of the normal appearing hilar vessels and peripheral vascular tree.

plus increased amplitude of pulsation of the pulmonary artery segment on the left mid-cardiac silhouette, a normal vascular pattern extending outwards from each hilus, and minimal right ventricular hypertrophy. The findings were felt to be consistent with a pulmonic stenosis.

The patient was discharged to return in nine months. However, on February 7, 1953, he was admitted to another hospital with the history of having had a respiratory infection two weeks before admission lasting for four days, and a three day history of migratory arthritis involving the right elbow, wrist, and both shoulders and ankles. The temperature was 104.4° F. The cardiac findings were the same as those mentioned above. Elevation of the white blood cell count, increased sedimentation rate, and a shift of the differential count to the left were present. Blood culture showed hemolytic coagulase-positive staphylococcus.

The child developed dyspnea, wheezing without rales in the lungs, and enlargement of the liver. Roentgenographic examination of the chest revealed lobar pneumonia in the right upper lobe. The child improved on antibiotic therapy, digitalis and oxygen. However, on February 17, 1953, he had his first hemoptysis. This recurred on February 18, 1953, and was more severe. Bronchoscopy disclosed some inflammation of the right upper lobe bronchus. Hemoptysis occurred four times and was severe enough to require a blood transfusion for replacement.

On May 27, 1953, he was re-admitted to the State University of Iowa Hospitals. A review of the roentgenograms taken elsewhere revealed a left pulmonary artery aneurysm close to the hilus, as well as the previously described pneumonia. During the interval of six weeks he had no further trouble. The physical examination was unchanged from that given initially, but progress films of the chest now revealed a 3 by 2.5 cm. round mass in the left hilus and two somewhat indistinct round shadows in the right upper lobe, the latter being diminished in volume (Fig. 2). In addition there was prominence of the pulmonary artery segment and diminished peripheral vascular pattern. Fluoroscopy of the heart indicated 1–2 plus right venticular hypertrophy as well as increased amplitude of pulsation of the pulmonary artery without hilar dance. The round masses on the right and left side were pulsatile. Angiocardiography using 75 per cent neo-iopax was done and the representative films are shown in Figures 3 and 4. These demonstrate the aneurysms and the degree of attenuation of the peripheral vascular tree with irregularity in the lumina of several of the branches. The "pruning" effect peripherally and especially in the bases is well demonstrated. It was our impression that this boy had pulmonary hypertension and pulmonary vascular disease together with pulmonary artery aneurysms.

On June 5, 1953, cardiac catheterization was performed. This revealed high right ventricular pressure of 95–110/0–2 mm. Hg (mean 47 mm.), high proximal pulmonary artery pressure of 88–108.7–14 mm. Hg (mean 6 mm.), and low distal pulmonary artery pressure of 8–12/2–4 mm. Hg (mean 6 mm.). Right femoral artery blood sample was 84 per cent oxygenated. At that time 100 per cent oxygen was not administered to help rule out an intracardiac shunt. No definitive diagnosis was made from this examination.

On June 16, 1953, a right upper lobectomy was done. The patient was discharged one week later to return for further surgery on the left side. He returned on July 8, 1953, because of severe hemoptysis. A roentgenogram taken at that time is shown in Figure 5. On July 10, 1953, while on the operating table he suddenly died.

Pathologic examination of the removed right upper lobe and the autopsy protocol were reviewed by Dr. John R. Carter, Professor of Pathology at University Hospitals. In the right upper lobe the main arterial trunk was enlarged to form a saccular dilatation 2 cm. in diameter. It was continuous on one side with another aneurysm 2 cm. in diameter. The left pulmonary artery aneurysm was saccular and 3.7 cm. in diameter located approximately 1 cm. from the point at which the artery entered the lower lobe. The heart weighed 173 gm. The right and left ventricles were of the same thickness and measured 1 cm. The ductus arteriosus was obliterated, but there was probe patency of the foramen ovale. It was not considered to be functionally open.

The microscopic changes, aside from focal atelectasis and emphysema and subpleural edema, were primarily limited to the arteries and arterioles. Our present findings are similar to those reported elsewhere.[6,7,10,11,15,17,22,23,25,27,28]

The changes appeared patchy, with normal and abnormal vessels being seen in the same field. The most prominent alterations occurred

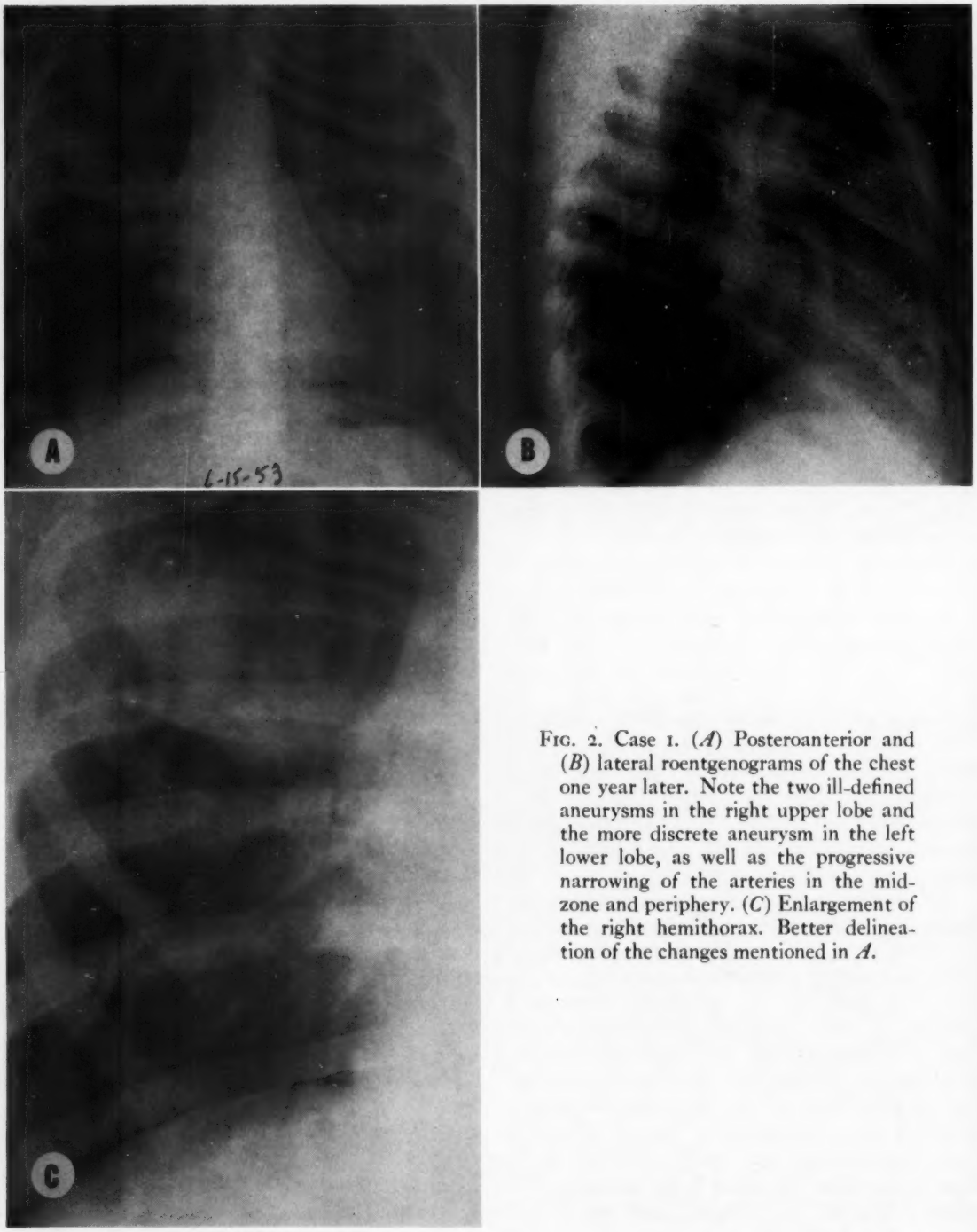


FIG. 2. Case 1. (*A*) Posteroanterior and (*B*) lateral roentgenograms of the chest one year later. Note the two ill-defined aneurysms in the right upper lobe and the more discrete aneurysm in the left lower lobe, as well as the progressive narrowing of the arteries in the midzone and periphery. (*C*) Enlargement of the right hemithorax. Better delineation of the changes mentioned in *A*.

subpleurally and involved principally the medium sized arteries and the arterioles. The alveolar wall capillaries did not show significant changes.

The changes in these vessels consisted of the following: (2) subintimal proliferation; (2) striking adventitial proliferation; (3) proliferation of the media with replacement of the smooth muscle by fibrous tissue; (4) fragmentation of elastic fibers involving both the internal and external lamellae. Many were duplicated. In some areas the elastic tissue was absent; (5) patchy swelling of the endothelial lining of the abnormal vessels; and (6) hypertrophy of the

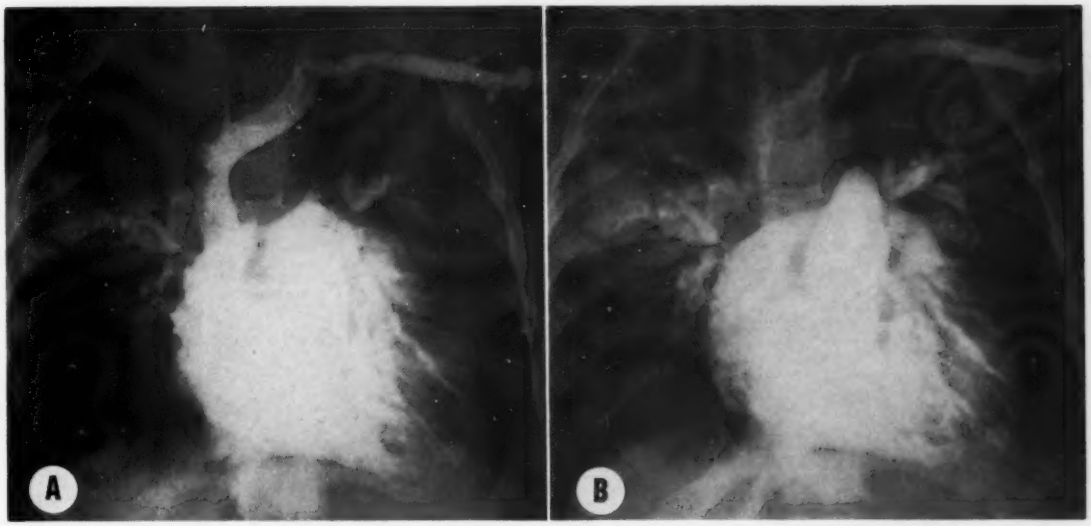


Fig. 3. Case 1. Angiocardiograms using 75 per cent neo-iopax. Films exposed (*A*) at 1.5 and (*B*) at 3 seconds. Note the "pruning" effect peripherally, the irregularity in the lumina of the arteries, the poor filling of the aneurysms, and the rapid attenuation of the peripheral vascular tree. These changes are indicative of the severe vascular lesions described in the text.

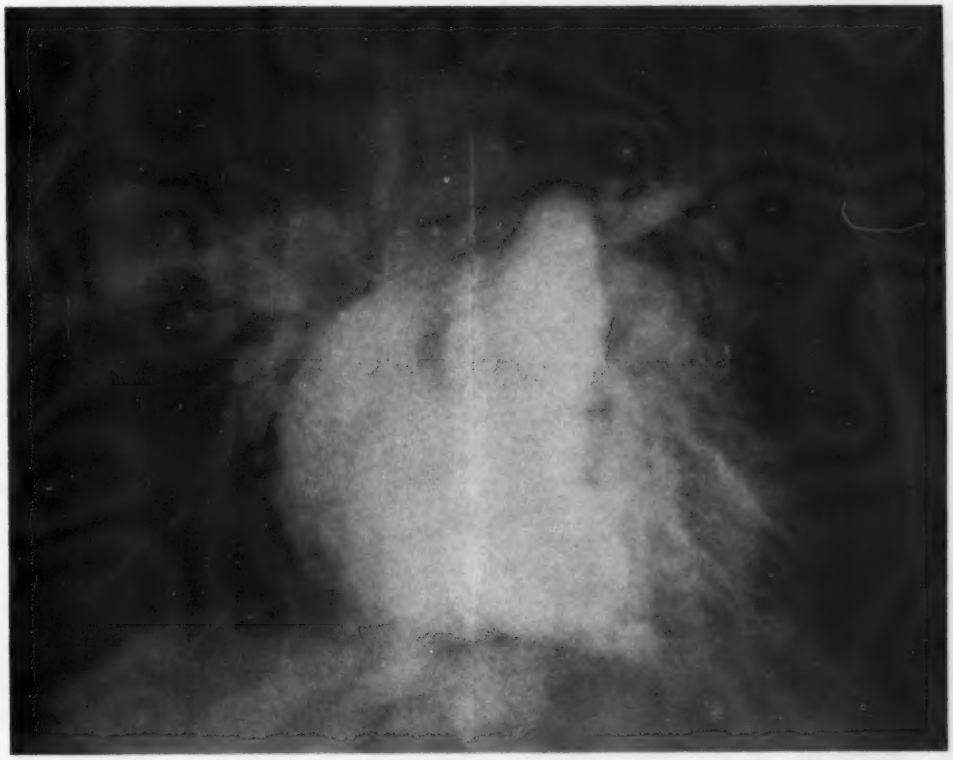


Fig. 4. Case 1. Enlargements of the right and left sides at 3 seconds. These demonstrate better the changes mentioned above.

FIG. 5. Case I. Posteroanterior roentgenogram of the chest taken just prior to death. Note the increasing cardiac size, the increasing size of the left pulmonary artery aneurysm and the progressively diminished vascular pattern.

muscle of the media of some of the vessels. The latter was not striking, but was present. Representative sections are shown in Figures 6 and 7.

Comment. This six year old boy had severe primary pulmonary hypertension complicated by multiple pulmonary artery aneurysms and minute patent foramen ovale, similar to those reported previously.[1,13,16] The desaturation of the arterial blood (84 per cent) might have been due either to a small right to left shunt through the foramen ovale, or, in this case, might be explained on the basis of uneven blood flow through the several aneurysms where ventilation is irregular and incomplete. In spite of the low arterial saturation, no clinical cyanosis was detected. Douglas, *et al.*[11] have reported microscopic aneurysms in a case of secondary pulmonary hypertension due to a patent ductus arteriosus, but this is the first time that roentgenographically demonstrable multiple pulmonary aneurysms occurring with this disease have been recorded. These accounted for the repeated and severe hemoptyses noted in this patient. Smaller aneurysms may well account for the hemoptyses noted in other reported cases. The angiograms are diagnostic and correlate well with the degree of pulmonary hypertension and with the lesions of the pulmonary vessels.

CASE II. D.W., male, aged four when first seen at the State University of Iowa Hospitals,

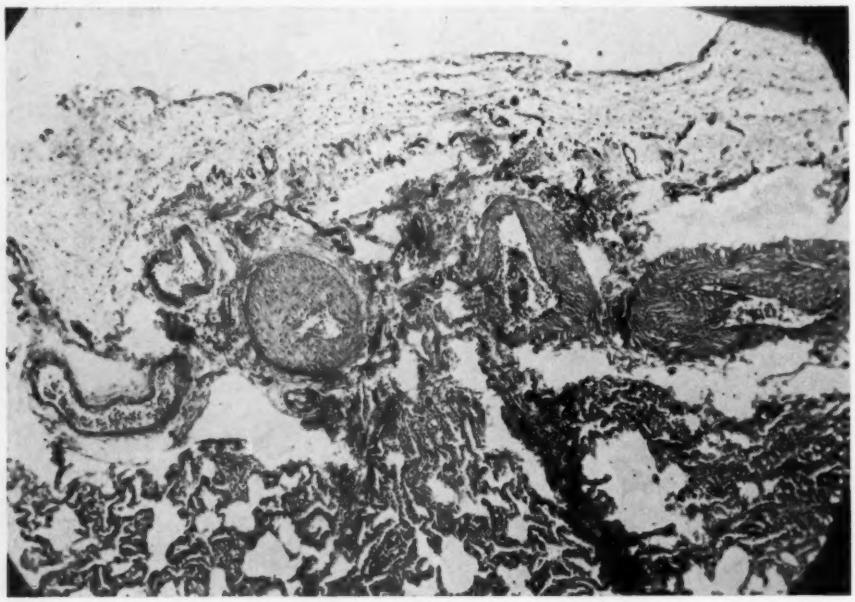


FIG. 6. Case I. Note the sclerosis of the subpleural arterioles and the difference between the sclerotic vessels and the normal ones on the left.

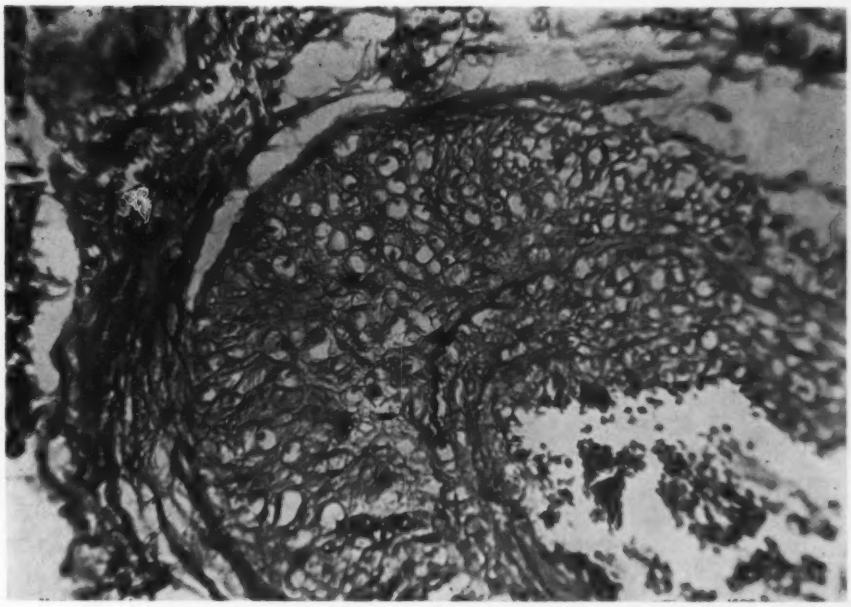


Fig. 7. Case 1. High power view of a sclerotic vessel (elastic tissue stain). Note the splitting of the internal elastic lamella with subintimal fibrosis. In addition, there is sclerosis and muscular hypertrophy of the media.

was born on July 9, 1950. Pregnancy and labor were normal. The birth weight was 5 pounds. The child was brought in by his mother since she felt that he acted like his brother. He was reported as being very quiet, liking to play in a squatting position and not running much. He turned blue when he became hot. A heart murmur was first noticed in January of 1954, apparently at the time of a pneumonia.

On July 22, 1954, when he was first seen at University Hospitals, aside from low normal weight and height standards, the positive physical findings were restricted to the heart. Whereas there was no cardiac enlargement, there was a Grade II or III harsh systolic murmur in the pulmonic area. Splitting of the second pulmonary sound was present, but its intensity was normal. A systolic thrill was noted in the neck vessels. There was no enlargement of the liver, no ascites and no cyanosis. Electrocardiogram was consistent with right ventricular hypertrophy.

Fluoroscopic and roentgenographic examination of the heart and lungs revealed 1 plus prominence of the pulmonary artery segment, as well as increased amplitude of pulsation of it. The vascular pattern extending outwards from each hilus appeared normal. No significant right ventricular enlargement was felt to be present at this examination. Our impression was that of pulmonic stenosis. The roentgenograms are seen in Figure 8.

On July 25, 1954, angiocardiography using 70 per cent urokon was done. The findings are demonstrated well in Figures 9 and 10. There is no evidence of shunt. The upper lobe vessels are normal in size and attenuate normally, simulating a leafy bush. The lower lobe vessels, however, are abnormal and have irregular and segmental narrowing of the vessel lumina. The peripheral branches are small, cut-off, or "pruned," particularly on the left, simulating a denuded shrub. These findings are not as pronounced as those of his brother. Our impression was that this boy, too, had primary pulmonary hypertension with moderately severe changes in the vessels, but without aneurysm formation.

On July 29, 1954, cardiac catheterization was performed. This revealed a right ventricular pressure of 58/9 mm. Hg, a pulmonary artery trunk pressure of 58/10 mm. Hg (mean 35 mm.), and a distal pulmonary artery pressure of 15/0 mm. Hg (mean 9 mm.). The arterial saturation was 95 per cent and increased to 100 per cent when he breathed 100 per cent oxygen. This indicated that there was no evidence of an intracardiac shunt from right to left. An interesting observation was made at the time of catheterization. This consisted of an

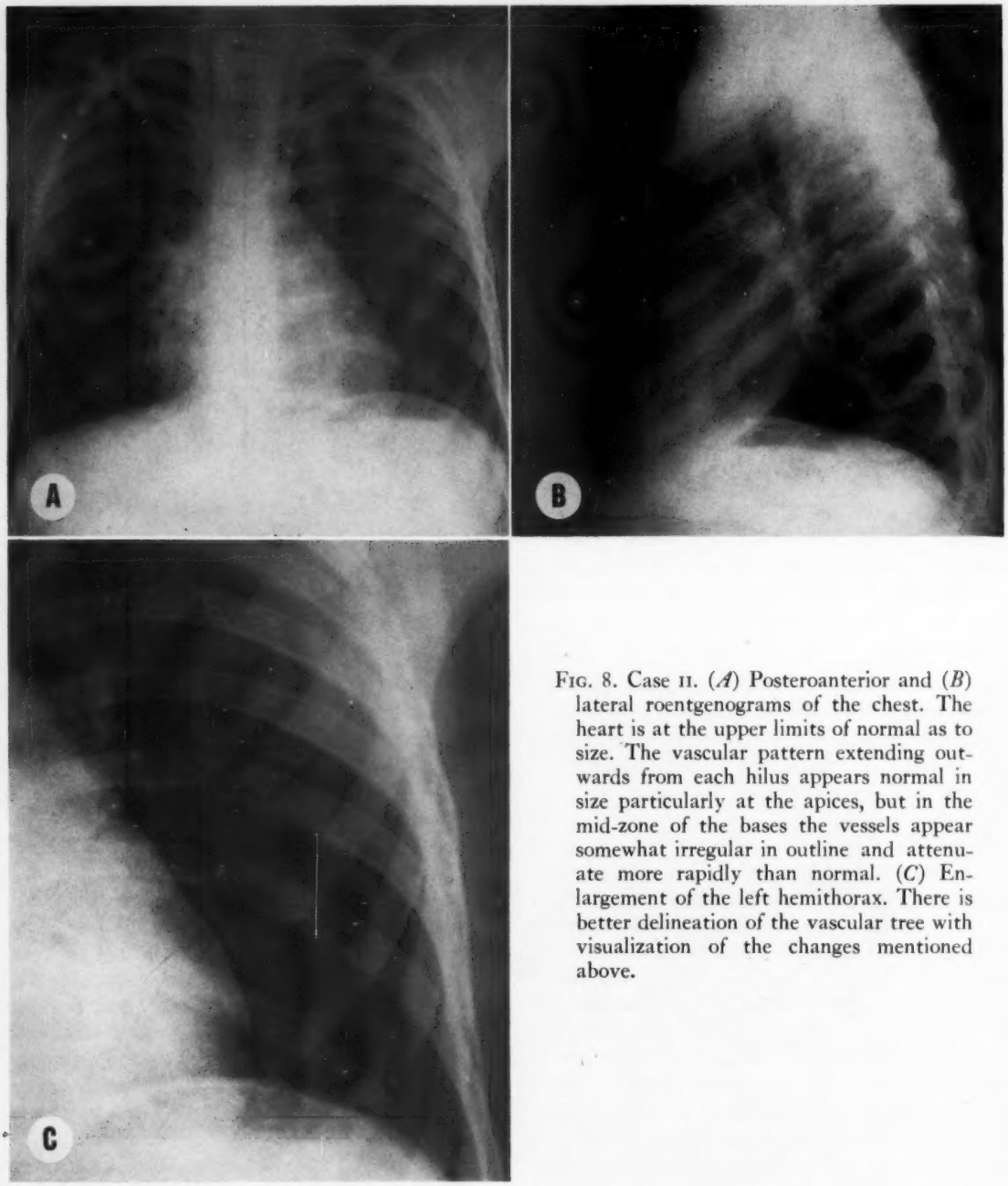


FIG. 8. Case 11. (*A*) Posteroanterior and (*B*) lateral roentgenograms of the chest. The heart is at the upper limits of normal as to size. The vascular pattern extending outwards from each hilus appears normal in size particularly at the apices, but in the mid-zone of the bases the vessels appear somewhat irregular in outline and attenuate more rapidly than normal. (*C*) Enlargement of the left hemithorax. There is better delineation of the vascular tree with visualization of the changes mentioned above.

intermittent obstruction to the passage of the catheter as though it were passing through irregularly narrowed arteries. The diagnosis by the cardiovascular laboratory was pulmonary hypertension, cause unknown.

Comment. This four year old boy has moderately severe pulmonary hypertension. The clinical, physical and roentgenographic evaluation of this patient indicates a similar disease process as that presented by his brother but of a less severe degree. Evans[16] and Wood [28] suggested that this disease process may be due to an inherent defect or to a congenital abnormality of the vascular tree, but Dresdale, *et al.*[13] were the first to report a family that fulfilled the criteria for primary pulmonary hypertension. Dyspnea unrelated to effort, but

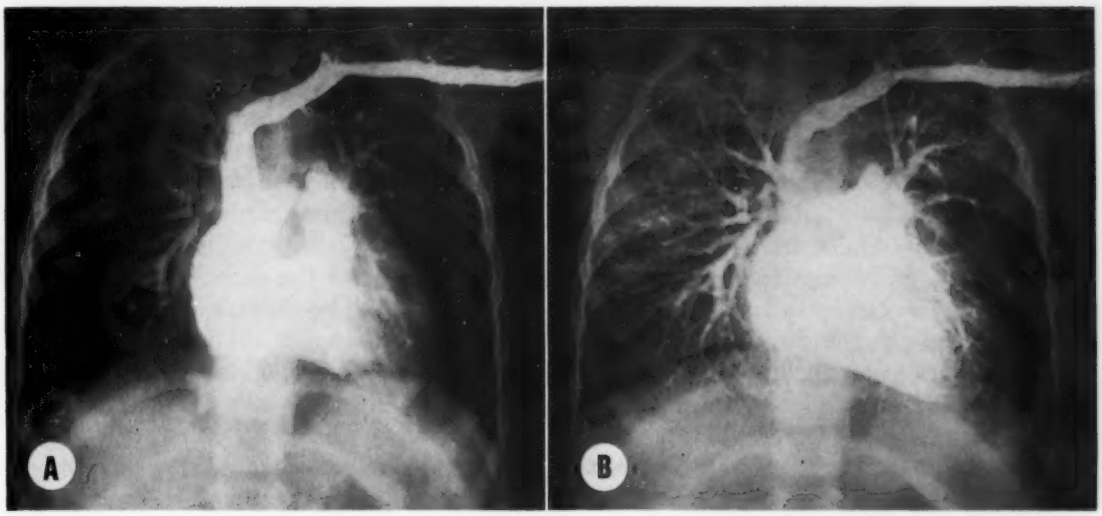


Fig. 9. Case 11. Angiocardiograms using 70 per cent urokon. Films exposed (*A*) at 1.5 and (*B*) at 3 seconds. Note the slight but definite irregularity in the lumina of the arteries just as they leave the hilus. There is normal arborization at the apices (leafy appearance) and on the right, but at the left base the attenuation is more rapid and abrupt, giving a "pruned" appearance to the vascular tree. Compare with Figures 3 and 4.

related to ambient temperature, has been reported by Fashena in a discussion of that paper. Perhaps a similar factor acted in the production of cyanosis in this child.

On February 16, 1955, this child was re-examined. No change in either the physical or roentgenographic examinations over the initial one was noted. A younger sister and brother have been examined and found to be normal.

DISCUSSION

Primary pulmonary hypertension in its earliest phase may be due to increased

Fig. 10. Case 11. Enlargements of the right and left sides at 3 seconds. These demonstrate better the changes mentioned above.

vascular tone or to resistance in the precapillary vascular bed, and not to any structural change in the vessels. This is particularly significant in explaining the occasional case in which at autopsy no lesions are found to account for the pulmonary hypertension. Studies by Dresdale, *et al.*[13] in primary pulmonary hypertension and Davies, *et al.*[9,10] in mitral stenosis using priscoline and hexamethonium respectively, would confirm this and implicate the autonomic nervous system at least early, or as a continuing force acting for an indefinite time, since they both were able to produce fall in pulmonary arterial pressure, especially with priscoline, as well as a concomitant increase in blood flow and symptomatic improvement in patients. With priscoline the patients showed a significant increase in cardiac output and a definite decrease in the calculated pulmonary vascular resistance. Resistance, therefore, can be modified by therapy. Further studies are indicated to evaluate the results of treatment and to elaborate, if possible, the etiology of this disease. Whereas a congenital defect or inherent abnormality in the vascular tree has been suggested, the report of Dresdale and his co-workers[13] and this present one are the only reports to date where a family relationship is present. It would seem likely that with continuing interest, more and more families will be found to have this disease, a disease not unlike that involving the greater circulation.

Pediatricians and radiologists must remember that at least 17 children to date, varying in age from twenty months to fifteen years have been reported as having primary pulmonary hypertension. The sex ratio is about equal in those cases in which the sex was stated. The symptoms in children may be unrevealing, but a high index of suspicion must be given to dyspnea and exercise coughing. The symptoms given for adults may or may not be present in children.

When pulmonary hypertension has progressed to the point of producing symptoms, the changes in the heart and pulmonary vessels can be demonstrated at fluoroscopy, on roentgenograms and on angiocardiograms. However, the similarity to pulmonic stenosis is striking. A differential diagnosis between pulmonic stenosis and pulmonary hypertension may not only be difficult but impossible, even with angiocardiography, unless cardiac catheterization is done. The severity of the findings correlates well with the degree of pulmonary hypertension. The fluoroscopic evidence in our cases consisted of the following: prominence of the pulmonary artery segment on the left side of the heart, increased amplitude of pulsation of the pulmonary artery trunk, similar to that seen in pulmonic stenosis, slight right ventricular enlargement, and minimal prominence of the hilar vessels and with normal or smaller than normal vessels in the periphery, particularly at the bases. The rapid attenuation of the peripheral branches of the pulmonary arteries is best seen on inspection of films. The "pruning" effect is more pronounced in the bases, and unless the pulmonary hypertension is severe and prolonged, is not seen in the apices. Correlation can be made between the degree of pulmonary artery pressure and the vascular pattern in the lungs, *e.g.*, the higher the pressure in the pulmonary artery the more proximally is the attenuation located and the larger the hilar vessels.[5,9,10,16] On angiocardiograms the pulmonary vasculature, in addition to the rapid attenuation and the irregularity of the lumina of the vessels, showed a "pruning" effect described by Evans[16] as follows: "pruning of the terminal branches of the pulmonary tree giving it an appearance of a denuded shrub in winter contrasting with the leafy bush in spring which typifies the healthy circulation."

We have not seen lines B of Kerley[24] in our cases. They have been described as occurring in mitral stenosis. Carmichael, *et al.*[5] and Davies and co-workers[9] have been able to correlate these lines with the degree of arterial pressure in the pulmonary circuit. For that reason search should be made for them in all cases of pulmonary hypertension.

Cyanosis, when it occurs in these cases,

has been explained on the basis of an intracardiac shunt such as a patent foramen ovale.[1,13] One of our cases, as well as 4 others reported in the literature, had such a defect. Usually they were quite small, admitting only the tip of a probe, and in our case, the defect was not considered to be physiologically patent. Ordway in a discussion of the paper of Bauersfeld, *et al.*[1] mentioned a case in which there was no cyanosis, yet there was arterial unsaturation. At autopsy no patent foramen ovale or other cardiac defect was found. He postulated that the flow of blood was through the bronchial capillaries. Nadas in a discussion of the same paper stated that Farber found an arteriovenous aneurysm which established a communication between the pulmonary arteries through a bronchial artery and then into a systemic artery without going to the alveoli. This could account for the cyanosis. In our patient (Case 1) we have two possible mechanisms; a patent foramen ovale, and the multiple aneurysms of the pulmonary arteries.

The cause of hemoptysis, which is an uncommon symptom in the over-all clinical picture of this disease, may be explained by microscopic aneurysms. In our case the severe hemoptyses were due to large multiple aneurysms of the pulmonary arteries.

The microscopic and angiocardiographic descriptions of the pulmonary vascular lesions, if taken alone and not correlated with the findings in the heart and lungs and with the patient's history, will not differentiate between primary and secondary pulmonary hypertension. The changes in the vessels represent the response of the pulmonary vascular bed to a stimulus which may be recognized (secondary) or which may be unknown (primary).

SUMMARY

1. Primary pulmonary hypertension as an entity must be differentiated from the secondary type due to recognized causes by careful attention to the clinical, roentgenographic, cardiac catheterization, and autopsy findings. Radiologists can exclude many of the causes of secondary hypertension, and, thus, they are in a position to recognize the primary type.

2. Two cases of primary pulmonary hypertension occurring in brothers aged six and four years are discussed. The older boy had severe hemoptyses from multiple pulmonary artery aneurysms, and at autopsy a probe-patent foramen ovale was found. The younger boy has definite but minimal clinical symptoms and roentgen findings. This is the first time that demonstrable aneurysms of the pulmonary arteries have been reported and the second time that a familial occurrence of this disease has been found.

3. The role of pulmonary arteriovenous communications in the production of cyanosis and desaturation of arterial blood without cyanosis and the role of microscopic aneurysms in the production of hemoptysis are discussed.

4. Seventeen cases of primary pulmonary hypertension occurring in children ranging in age from twenty months to fifteen years have been previously reported. Included in these reports are at least 4 cases associated with patency of the foramen ovale.

5. The vascular lesions demonstrable on angiocardiography and at autopsy represent the response of the pulmonary vascular bed to a stimulus which may be recognized (secondary) or which may be unknown (primary).

State University of Iowa
Iowa City, Iowa

ADDENDUM

Since the above paper was given (September, 1955), an article on this same disease has been published in the *Acta radiologica*, 1955, *44*, 209–216, by H. Arvidsson, J. Karnell, and T. Möller on "Multiple Stenosis of the Pulmonary Arteries Associated with Pulmonary Hypertension Diagnosed by Selective Angiocardiography." Similar findings are present in our Case 1, although not as well demonstrated by venous angiocardiography as by the selective method given in that paper.

It should also be added that Case 11 of our series has been examined recently. There are no symptoms or signs to indicate any progression of the pulmonary vascular lesions originally described.

REFERENCES

1. BAUERSFELD, S. R., MACDONALD, A. J., BERTHRONG, M., and TAUSSIG, H. B. Primary pulmonary hypertension. *Am. J. Dis. Child.*, 1952, *84*, 765–767.
2. BEDFORD, D. E. Discussion on pulmonary heart disease. *Proc. Roy. Soc. Med.*, 1951, *44*, 597–603.
3. BRANWOOD, A. W. Primary pulmonary hypertension. *Edinburgh M. J.*, 1954, *61*, 332–341.
4. BRINTON, W. D. Primary pulmonary hypertension. *Brit. Heart J.*, 1950, *12*, 305–311.
5. CARMICHAEL, J. H. E., JULIAN, D. G., JONES, G. P., and WREN, E. M. Radiological signs in pulmonary hypertension; significance of lines B of Kerley. *Brit. J. Radiol.*, 1954, *27*, 393–397.
6. CHRISTIAN, E. R. Hepatic death in young man with occult pulmonary arteriosclerosis and right heart failure (Ayerza's disease). *Am. Rev. Tuberc.*, 1954, *70*, 1083–1091.
7. CROSS, K. R., and KOBAYASHI, C. K. Primary pulmonary vascular sclerosis. *Am. J. Clin. Path.*, 1947, *17*, 155–162.
8. CUTLER, J. G., NADAS, A. S., GOODALE, W. T., HICKLER, R. B., and RUDOLPH, A. M. Pulmonary arterial hypertension with markedly increased pulmonary resistance. *Am. J. Med.*, 1954, *17*, 485–498.
9. DAVIES, L. G., GOODWIN, J. F., STEINER, R. E., and VAN LEUVEN, B. D. Clinical and radiological assessment of pulmonary arterial pressure in mitral stenosis. *Brit. Heart J.*, 1953, *15*, 393–400.
10. DAVIES, L. G., GOODWIN, J. F., and VAN LEUVEN, B. D. Nature of pulmonary hypertension in mitral stenosis. *Brit. Heart J.*, 1954, *16*, 440–446.
11. DOUGLAS, J. M., BURCHELL, H. B., EDWARDS, J. E., DRY, T. J., and PARKER, R. L. Systemic right ventricle in patent ductus arteriosus; report of case with obstructive pulmonary lesions. *Proc. Staff Meet., Mayo Clin.*, 1947, *22*, 413–423.
12. DRESDALE, D. T., SCHULTZ, M., and MICHTOM, R. J. Primary pulmonary hypertension; clinical and hemodynamic study. *Am. J. Med.*, 1951, *11*, 686–705.
13. DRESDALE, D. T., MICHTOM, R. J., and SCHULTZ, M. Recent studies in primary pulmonary hypertension including pharmacodynamic observations on pulmonary vascular resistance. *Bull. New York Acad. Med.*, 1954, *30*, 195–207.
14. Editorial. Pulmonary hypertension. *Lancet*, 1955, *1*, 136–138.
15. EDWARDS, J. E. Structural changes of pulmonary vascular bed and their functional significance in congenital cardiac disease: Twenty-sixth Ludvig Hektoen Lecture. *Proc. Inst. Med. Chicago*, 1950, *18*, 134–146.
16. EVANS, W. Congenital pulmonary hypertension. *Proc. Roy. Soc. Med.*, 1951, *44*, 600–608.
17. FERGUSON D. J., and VARCO, R. L. Relation of blood pressure and flow to development and regression of experimentally induced pulmonary arteriosclerosis. *Circulation Res.*, 1955, *3*, 152–158.
18. FERRER, M. L., and HARVEY, R. M. Etiology of secondary pulmonary hypertension. *Bull. New York Acad. Med.*, 1954 *30*, 208–220.
19. GRISWOLD, H. E., JR., LIUM, J. H., NASH, G. A., PITCAIRN, D. M., CONKLIN, W. S., GOSS, W. A., JR., and RENNIE, D. W. Primary pulmonary hypertension in children. Program, Twenty-fourth Scientific Session, American Heart Association, 1951.
20. HOWARTH, S., and LOWE, J. B. Mechanism of effort syncope in primary pulmonary hypertension and cyanotic congenital heart disease. *Brit. Heart J.*, 1953, *15*, 47–54.
21. MACCALLUM, W. G. Obliterative pulmonary arteriosclerosis. *Bull. Johns Hopkins Hosp.*, 1931, *49*, 37–48.
22. OWEN, W. R., THOMAS, W. A., CASTLEMAN, B., and BLAND, E. F. Unrecognized emboli to lungs with subsequent cor pulmonale. *New England J. Med.*, 1953, *249*, 919–926.
23. SAMUELSSON, S. Primary cor pulmonale; chronic cor pulmonale resulting from pulmonary hypertension of unknown etiology; review of literature; report of 4 cases. *Acta. med. scandinav.*, 1952, *142*, 177–189.
24. SHANKS, S. C., and KERLEY, P., Editors. Textbook of X-ray Diagnosis by British Authors. Volume II. Second edition. W. B. Saunders Company, Philadelphia, 1951, p. 404.
25. SILVER, A. W., KIRKLIN, J. W., ELLIS, F. H., JR., and WOOD, E. H. Symposium on physiologic, clinical and surgical interdependence in study and treatment of congenital heart disease; regression of pulmonary hypertension after closure of patent ductus arteriosus. *Proc. Staff Meet., Mayo Clin.*, 1954, *29*, 293–300.
26. WHITAKER, W. Clinical diagnosis of pulmonary hypertension in patients with mitral stenosis. *Quart. J. Med.*, 1954, *23*, 105–112.
27. WOLD, L. E. Pulmonary hypertension. *Journal-Lancet*, 1954, *73*, 341–342.
28. WOOD, P. Pulmonary hypertension. *Brit. M. Bull.*, 1952, *8*, 348–353.

Vol. 78, No. 3

GAS IN THE FETAL BLOOD STREAM*

A USEFUL SIGN OF FETAL DEATH

By ROBERT B. ENGLE, M.D.
PASADENA, CALIFORNIA

DETERMINATION of fetal death may be perplexing for both clinician and radiologist. Gas in the fetal circulatory system is a useful sign of fetal death. It was first described by Roberts[7] in 1944. The gas may delineate the heart, aorta, iliac vessels, umbilical and liver vessels, and has even been reported in the skull vessels of the stillborn infant. As a rule, the gas is readily seen in roentgenograms of the fetus in utero, and is usually best shown in the lateral projection. An upright view may show fluid levels within the heart. Roentgenograms of the stillborn infant will confirm the diagnosis if maternal intestinal gas has caused confusion. The accumulations of gas in the heart chambers and aorta give a characteristic appearance, and gas in branching vessels of the mesentery or liver can usually be distinguished from maternal intestinal gas. Autopsy performed under water will afford further proof of the presence of gas.

Only 32 cases of gas in the fetal blood stream have been reported previously. Although the vast majority of these have been reported since 1953, it is likely that the finding is relatively common. Crick and Sims,[1] for example, found fetal gas in 7 of 23 patients examined roentgenographically for evidence of fetal death during a seven month period at the Auckland Hospital, New Zealand. The 23 patients represented those having roentgenographic examinations out of a total group of 115 stillbirths during the period studied.

Free gas may precede other roentgen signs of death or may be the only sign that appears.[8] The gas may disappear before delivery or become reduced in amount.[1,6] Two of the reported cases demonstrated fetal gas within three days of the last time fetal heart tones were audible.[4,7] Other cases showed time intervals ranging from two to three weeks.

REPORT OF CASES

CASE 1. Mrs. E. D., St. Luke Hospital Case No. E1230, a thirty-seven year old white female, gravida v, para III, had had 2 previous pregnancies terminating in stillbirth of fetuses with erythroblastosis fetalis. Patient was Rh negative with elevated Rh blocking titer. On October 18, 1954, the eighth month of her present pregnancy, she had painless vaginal bleeding caused by marginal placenta previa. Examination showed fundus 30 cm. above symphysis and no fetal heart tones could be heard. Roent-

FIG. 1. Case 1. Lateral roentgenogram showing gas in the fetal heart chambers and in branching abdominal vessels which may represent ductus venosus.

* From the Department of Radiology, St. Luke Hospital and the University of Southern California School of Medicine.

FIG. 2. Case I. Enlargement of the area containing the gas shadows.

genograms on October 19, 1954, showed gas in the fetal blood vessels and heart (Fig. 1 and 2).

On October 26, 1954, there was a spontaneous delivery of a stillborn fetus. The fetus weighed 5 pounds, 13 ounces, and was macerated, necrotic, and foul-smelling. The autopsy was not conducted under water and gas was not demonstrated. Placenta showed changes consistent with erythroblastosis fetalis.

CASE II. Mrs. B. S., a twenty-four year old white female, gravida 1, para 0, had a normal, uneventful pregnancy until the thirty-fourth week of gestation when fetal heart tones could not be heard. Roentgenograms made on this date showed free gas in the heart, aorta, and in the umbilical veins of the fetus (Fig. 3). Patient was Rh positive.

Patient delivered spontaneously on November 20, 1954. The stillborn fetus was dusky and macerated. It weighed 7 pounds.

DISCUSSION

The cause of the development of gas in the blood stream of the dead fetus is not known. Crick and Sims[1] collected gas from the heart and blood vessels of 7 stillborn infants and identified the gas as nitrogen. They made bacteriologic studies of fetal blood, and the great majority yielded negative cultures. There are now a number of cases to suggest that Rh incompatibility is not responsible.[1,3] The determination by Crick and Sims that the gas in the circulatory system represents nitrogen is important in that it invalidates many theories regarding the origin of the gas. Their work has not been confirmed by others, and further studies are desirable.

Samuel and Gunn[8] advance the interesting theory that gas embolus may be the *cause* of death. Intracardiac gas was present in all 15 of their cases. They also showed gas in the umbilical cord vessels in earlier roentgenograms which was not present on subsequent films. Thus, they postulate that gas passes from the placenta via the umbilical cord into the fetal vascular tree. They ascribe this gas passage to a func-

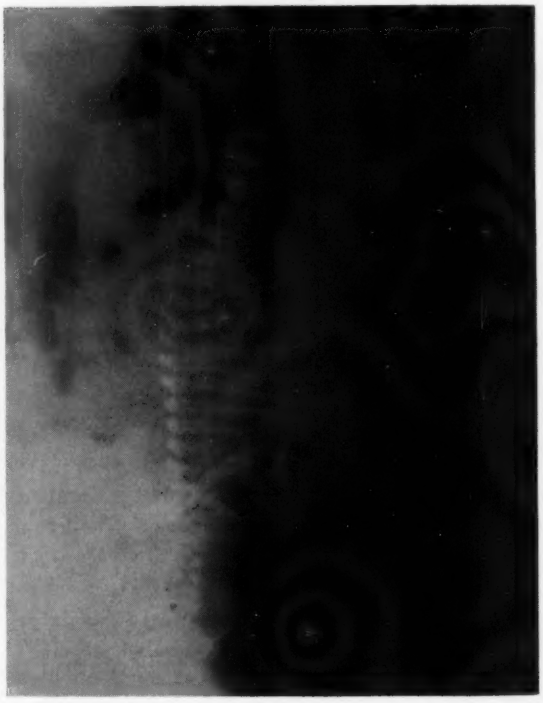


FIG. 3. Case II. Lateral roentgenogram showing gas in the fetal heart chambers, aorta, and in large caliber vessels which probably represent umbilical veins.

tional alteration of the placenta, as in Rh incompatibility, with a differential pressure gradient between maternal and fetal circulation.

SUMMARY

1. Free gas in the fetal blood vessels and heart is a valuable sign of fetal death.

2. The literature is reviewed and 2 additional cases of this condition are reported.

St. Luke Hospital
Pasadena 8, California

The author expresses his thanks to Dr. Austin Wilson for his permission to report Case II, which was seen and diagnosed by Dr. Wilson.

REFERENCES

1. Crick, A. F., and Sims, F. H. Gas within foetus indicating foetal death. *J. Fac. Radiologists*, 1953, *5*, 126–133.
2. Davidson, C. N. Roentgen demonstration of fetal death (gas within fetus) and uterine rupture; report of threee unusual cases. Am. J. Roentgenol. & Rad. Therapy, 1949, *62*, 837–842.
3. Holm, O. F. Free gas in fetal vessels as roentgenologic sign of intrauterine fetal death. *Acta radiol.*, 1954, *42*, 116–120.
4. Kettunen, K. Fetal death diagnosed roentgenographically by presence of gas in fetal circulatory system. *Acta radiol.*, 1952, *37*, 81–84.
5. Margolis, A. J., and Jones, M. D. Gas within circulation of dead fetus in utero; report of 2 cases. *Obst. & Gynec.*, 1954, *3*, 631–636.
6. Riemenschneider, E. A. Gas in fetal circulation: Sign of fetal death; case report. *Ohio State M. J.*, 1955, *51*, 139.
7. Roberts, J. B. Gas in fetal circulatory system as sign of intrauterine fetal death. Am. J. Roentgenol. & Rad. Therapy, 1944, *51*, 631–634.
8. Samuel, E., and Gunn, K. Gas embolus as roentgen sign of fetal death. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1955, *73*, 974–978.
9. Tager, S. N. New roentgen sign of fetal death. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1952, *67*, 106–110.

DELAYED CYSTOGRAPHY IN CHILDREN*

By HAROLD FULTON, M.D
DETROIT, MICHIGAN

IT IS generally conceded that reflux of urine from the urinary bladder into the ureter rarely occurs in normal, unanesthetized humans. Vesicoureteral reflux, when it does occur, is considered a potent factor in upper urinary tract infection. This is particularly true in infants and children.

Roentgenologic demonstration of vesicoureteral reflux has been accomplished in several ways:

Retrograde Cystography or Urethrocystography. This is the simplest method, roentgenograms being exposed during or directly following introduction of contrast medium into the bladder per urethra or by urethral catheter. Ureteral filling by the contrast agent may be observed immediately, but if such filling does not occur ureteral reflux is assumed to be absent.

Voiding Cystography. After the bladder has been filled with contrast medium from below and roentgenograms of the distended bladder exposed, further film studies are made during the act of micturition. A higher yield of positive evidence of ureteral reflux is obtained than with the simple cystography.

Postvoiding Cystography. In infants and small children it is impractical to expect conscious control of voiding for roentgenographic purposes, and it is time-consuming as well as frustrating to await fortuitous voiding by the child. Therefore, after contrast medium has been instilled in the bladder by catheter and the proper cystograms made, the catheter is withdrawn. If some degree of bladder distention has been achieved by the contrast instillation, removal of the catheter (plain or indwelling) will stimulate urination. Exposures made immediately after voiding will serve to demonstrate ureteral reflux in some cases where it was not elicited by the prevoiding cystogram.

Lipiodol Ascent. Young, Anderson, and King[7] recently reported the use of ascendant lipiodol for the demonstration of residual bladder urine. Incidentally, in some of the children studied, the ascendant lipiodol (containing less iodine by weight than the usual lipiodol compound) refluxed into the pyelocalyceal system. The reflux was revealed on roentgenograms exposed twenty-four to forty-eight hours after the introduction of lipiodol into the bladder. The disadvantage of this unique method of proving vesicoureteral reflux is that the offending ureter, is not completely outlined as with the water-soluble contrast media.

Delayed Cystography. In 1948, Stewart,[4] of Los Angeles, demonstrated ureteral reflux roentgenographically in a patient in whom exposure of routine retrograde cystographic films was inadvertently delayed for about one-half hour. He quickly adapted this technique of "delayed cystography" to pediatric problem cases with interesting results. Bunge[1,2] has also employed delayed cystography extensively, and emphasizes its value in children.

In 1955, Stewart[5] reviewed his seven years' experience with delayed cystography and reached the following pertinent conclusions:

1. The degree to which the bladder is distended with contrast medium evidently bears no relation to whether or not ureteral reflux will occur.

2. Reflux does not occur in the normal urinary tract. It occurs in some cases in which the pathologic cause may not be demonstrated.

3. It is impossible to predict competence or incompetence of a ureteral orifice on the basis of its cystoscopic appearance.

4. If vesicoureteral reflux does not occur during delayed cystography, it may occur during the act of voiding. In some patients

* Presented at the Fifty-seventh Annual Meeting of the American Roentgen Ray Society, Los Angeles, California, September 25–28, 1956.

reflux may be evident during delayed cystography and it will not occur during voiding. Reflux has been proved to occur only during micturition in a few patients.

In the past three years, in cooperation with the Urology Staff of Harper Hospital, we have performed delayed cystography in a number of children, most of whom suffered from recurrent upper urinary tract infection, the etiology and nature of which had not yet been determined by the routine urographic diagnostic procedures.

TECHNIQUE FOR DELAYED CYSTOGRAPHY

Delayed cystography is best performed without resort to general anesthesia. Local anesthesia may be used, but is rarely necessary in infants and female children, the latter being particularly subject to this examination.

After a survey roentgenogram of the abdomen and pelvis has been exposed and viewed, the contrast medium—5 per cent sodium iodide or other water-soluble agent—is injected by increments into the urinary bladder, usually through a small Foley-type retention catheter. When the child begins to complain of discomfort or when a maximum of 150 cc. of the medium has been instilled, the catheter is clamped. Serial cystograms are then made at 5, 10, 20, 30, 45 and 60 minutes. The multiple films are quite necessary as reflux may be recognized at one interval and be absent at the next. After the one hour cystogram has been made, the catheter is withdrawn from the bladder, usually stimulating spontaneous voiding by the child. When voiding has been completed, a postvoiding cystogram is immediately taken.

Most children lie quietly during the entire procedure, but free movement on the examination table is allowed.

The following 3 selected cases illustrate the value of delayed cystography.

REPORT OF CASES

Case 1. This seven year old girl had recurrent attacks of right abdominal pain and three previous episodes of urinary tract infection characterized by frequency, urgency and fever. Cystoscopy revealed an inflamed bladder containing thick pus. The ureteral orifices appeared normal and the ureters catheterized easily. Retrograde pyelograms demonstrated moderate pyelectasis and ureterectasis on the right side (Fig. 1). A discrepancy between the size of the renal collecting system and the renal parenchyma suggested the possibility of double renal pelvis. Delayed cystogram (Fig. 2) showed immediate reflux of the contrast medium into the dilated right ureter and pyelocalyceal system. The degree of dilatation of these structures appeared greater than on the retrograde pyelogram.

Fig. 1. Case 1. Retrograde pyelogram showing mild pyelectasis and ureterectasis of lower one-half of a double right kidney.

A heminephrectomy was performed (Dr. F. B. Bicknell). Bifurcation of the right ureter in its upper third was encountered, with a normal caliber ureter serving the upper hemipelvis of the kidney and a large atonic dilated ureter extending from the dilated lower hemipelvis toward the urinary bladder.

Fig. 2. Case I. Delayed cystogram (30 minute interval) showing marked reflux into the dilated right ureter and pyelocalyceal system. The dilatation appears greater than on the retrograde pyelogram.

The surgical specimen, consisting of the lower half of the right kidney, the corresponding pelvis and dilated ureter segment from the ureteropelvic junction to the point of ureteral fusion, exhibited microscopically chronic pyelonephritis and ureteritis.

Postoperatively the child has been free of urinary tract symptoms, and a delayed cystogram exposed nine months postoperatively showed persistent reflux into the distal portion of the right ureter which had postoperatively diminished somewhat in size.

Case II. This seven year old girl had a history of urinary frequency since the age of three years; also, episodes of temperature elevation (up to 103° F.), at which time the urine was offensive to smell. She did not have back pain or hematuria.

Cystoscopy (Dr. M. S. Mahlin) revealed a large caliber stricture of the urethra. Bladder capacity was normal. Both ureteral orifices appeared normal and catheterized easily. Trigonitis cystica was noted.

Retrograde pyelograms showed no abnormality of the pyelocalyceal systems or ureters (Fig. 3).

A delayed cystogram showed no ureteral reflux up to sixty minutes (Fig. 4). The postvoiding roentgenogram, however, showed the bladder partially empty and considerable reflux of contrast medium into the left ureter and pyelocalyceal system was demonstrated (Fig. 5). No reflux was shown on the right side.

The urethral stricture was dilated, and since treatment no symptoms of urinary tract infection have been noted.

Case III. This four year old girl had enuresis and incontinence since birth. A spina bifida occulta and low back hemangioma were treated surgically at the age of six months. Development of the child progressed normally. She walked at the age of one year. There was no history of fever or signs of urinary tract infection.

Cystoscopy (Dr. F. B. Bicknell) revealed a

Fig. 3. Case II. Retrograde pyelogram demonstrating no abnormality of the upper urinary tract.

bladder capacity of 100 cc. Inflammatory reaction of the bladder neck and urethra was prominent. The ureteral orifices appeared patulous; this was especially evident of the left orifice. Both ureters catheterized with ease.

Retrograde pyelograms showed no abnormality of the upper urinary tract (Fig. 6).

A delayed cystogram revealed marked trabeculation of the bladder wall with cellule formation. Up to one hour no vesicoureteral reflux was demonstrated (Fig. 7). At one hour, however, a definite reflux into the right ureter and pyelocalyceal system was shown (Fig. 8).

Cystometrogram demonstrated an uninhibited or hypertonic bladder.

The patient's parents were instructed concerning a routine of frequent (every two hours) urination for the child, with some improvement of continence.

DISCUSSION

Uteral reflux as observed roentgenologically is of several types (Table 1).

Immediate vesicoureteral reflux can be

Fig. 5. Case II. Delayed cystogram, postvoiding. Vesicoureteral reflux on the left side. Slight dilatation of the left ureter and pyelocalyceal system not demonstrated on retrograde pyelogram.

Fig. 4. Case II. Delayed cystogram (45 minute interval). No ureteral reflux.

Fig. 6. Case III. Retrograde pyelogram. Normal appearance of the upper urinary tract.

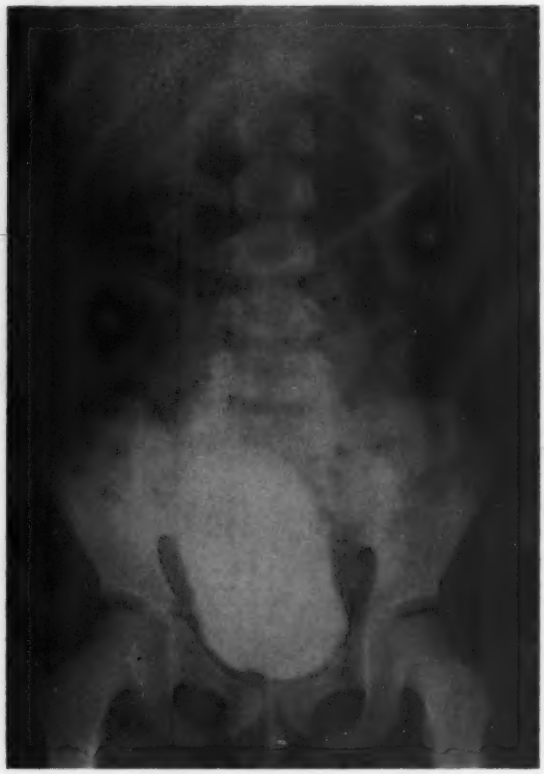


Fig. 7. Case III. Delayed cystogram (10 minute interval). No ureteral reflux.

demonstrated by simple cystography. The reflux is considerable in amount, predominantly bilateral and usually sustained. This type of reflux is frequently encountered in children with neuromuscular uropathy or with chronic bladder neck obstruction. Delayed cystography or voiding cystography is not necessary for demonstration of this immediate type of reflux.

Table I

VESICOURETERAL REFLUX

I.	Immediate, sustained
	A. Unilateral
	B. Bilateral
II.	Delayed, sustained or recurrent
	A. Unilateral
	B. Alternatingly unilateral
	C. Bilateral
III.	Voiding
	A. Unilateral
	B. Bilateral
IV.	Occasional—transient, not reproducible; no dilatation of ureter or pyelocalyceal system

Delay in vesicoureteral reflux may extend up to three hours, according to Stewart and Bunge. Few instances will be overlooked, however, if delayed cystograms are exposed at fairly frequent intervals up to one hour. This delayed reflux may be unilateral, bilateral, or alternatingly unilateral; sustained or recurrent. It is reproducible—that is, it can be re-demonstrated at will as long as the underlying uropathy persists. The volume of refluxed urine varies from a minimal amount seeping into the lower ureter to a large quantity distending the entire ureter and pyelocalyceal system. In this latter respect the incongruence of the excretory or retrograde pyelographic appearance of the pyelocalyceal system and that obtained by delayed cystographic reflux is noteworthy (Case II). St. Martin *et al.*,[6] for instance, report that in 14 patients with marked vesicoureteral reflux

Fig. 8. Case III. Delayed cystogram (60 minute interval). Vesicoureteral reflux on the right side.

only 3 were considered to have abnormal excretory urograms. The delayed cystogram then is particularly valuable in those pediatric patients where intermittent urinary infection is unexplained by the results of cystourethroscopy, excretory urography and retrograde pyelography. The demonstration of startling degrees of vesicoureteral reflux, revealed by delayed cystography in many such patients, leads to a new therapeutic approach often with satisfying results, as attested by Stewart and Bunge.

Ureteral reflux elicited by voiding or postvoiding cystography does not differ in nature or significance from the reflux shown during delayed cystography.

It must be admitted that rarely vesicoureteral reflux can occur in a normal infant or child. This "occasional" reflux is easily distinguished from the significant varieties —it is unilateral, transient, usually not reproducible and unassociated with dilatation of the ureter or pelvis. Such "occasional" ureteral reflux has been induced in only 1 of 50 healthy infants by Iannaccone and Panzironi,[3] and in that one case the authors note that (1) the ureteral reflux was unilateral, (2) the ureter and pelvis appeared normal, (3) there was quick disappearance of the contrast medium from the pelvis and ureter, and (4) no reflux was demonstrable, although carefully sought for under various degrees of bladder filling at the same session and two weeks later.

SUMMARY

Vesicoureteral reflux is an important factor in infections of the upper urinary tract in infants and children. Delayed cystography is one method for demonstrating such reflux which may be of assistance in solving some problem cases of pediatric urology.

Harper Hospital
Detroit 1, Michigan

REFERENCES

1. Bunge, R. G. Delayed cystograms in children. *J. Urol.*, 1953, *70*, 729–732.
2. Bunge, R. G. Further observations with delayed cystograms. *J. Urol.*, 1954, *71*, 427–434.
3. Iannaccone, G., and Panzironi, P. E. Ureteral reflux in normal infants. *Acta radiol.*, 1955, *44*, 451–456.
4. Stewart, C. M. Delayed cystograms. *J. Urol.*, 1953, *70*, 588–593.
5. Stewart, C. M. Delayed cystography and voiding cystourethrography. *J. Urol.*, 1955, *74*, 749–759.
6. St. Martin, E. C., Campbell, J. H., and Pesquier, C. M. Cystography in children. *J. Urol.*, 1956, *75*, 151–159.
7. Young, B. W., Anderson, W. L., and King, G. G. Radiographic estimation of residual urine in children. *J. Urol.*, 1956, *75*, 263–272.

CHONDROANGIOPATHIA CALCAREA SEU PUNCTATA (CHONDRODYSTROPHIA CALCIFICANS CONGENITA): AN ATYPICAL, STATIONARY FORM OF THE DISEASE

By J. LICHT, M.D.,* *and* M. JESIOTR, M.D.†

SINCE the publication by Conradi[4] in 1914, about 30 cases of a new nosologic entity have been described in the literature under different headings, such as chondrodystrophia calcificans congenita, chondrodystrophia punctata, dysplasia epiphysialis punctata and chondroangiopathia calcarea seu punctata. This congenital anomaly, which may be familial, is characterized roentgenologically by multiple, small, spotty calcific deposits in the epiphyseal cartilages of the long bones of both extremities, as well as in the cartilaginous anlage of the small bones of the extremities and of the vertebrae (Hünermann,[10] Haynes and Wangner,[8] Paul[16]).

Most cases described in the literature showed no symptoms, and the changes were discovered accidentally during roentgen examination. In other cases associated anomalies such as one or more shortened extremities, contractions of joints in flexion, syndactylism, pes calcaneo-valgus, congenital cataract, etc., called attention to the possible co-existence of the anomaly.

The accompanying shortening of the extremities is the result of an endochondral ossification disorder and not of the calcific deposits found in the embryonic cartilages of the bones. Proof for this, as demonstrated by Paul[16] and others, is offered by the roentgenologic follow-up of these cases, showing that the calcific deposits disappear after a few years without signs of inhabited growth of the involved bones. This fact also serves as evidence that chondroangiopathia calcarea seu punctata is an isolated anomaly. To prevent confusion with fetal chondrodystrophy, the writers prefer to use the synonym "chondroangiopathia calcarea seu punctata" for its designation. The histologic findings were described in detail by Tisdall and Erb,[21] Cocchi,[3] and Coughlin, *et al.*[5] According to Raap[17] proliferation of the connective tissue of periosteal origin occurs, the deeper layers of which show cartilaginous character with formation of osteoid tissue, leading to partial calcification. Cocchi[3] found that the cartilage breaks up into multiple islands and that an abnormal vascularization forms in the epiphyseal cartilages and in the cartilaginous anlage of the small bones. The ending of each vessel becomes the center of a pathologic calcium deposit. The primary factor in this histopathogenesis is unknown, but there can be no doubt that we are dealing here with changes of perichondral character, whereas the changes in the other chondrodystrophies are of an enchondral nature. Mixed forms or, better, simultaneous appearance of both processes may occur, as is shown by a number of cases.

The etiology of chondroangiopathia calcarea seu punctata is likewise unknown and the blood chemistry as well as the thyroid function show no deviation from the normal worth mentioning, in contrast to the cretinoid epiphyseal dysgenesis in which there is a congenital hypothyroidism.

All the cases that have been reported so far were observed in the newborn and small children. The subjects who had a roentgenologic follow-up showed complete disappearance of the calcific deposits within the first three years of life, with normally progressive ossification of the epiphyses and of the short spongy bones of the extremities and of the vertebrae. Only in those instances in which there was association of an

* Labor Sick Fund, Central Polyclinic, X-Ray Department, Tel-Aviv, Israel.
† Hospital for Chest Diseases of the American Joint Distribution Committee, Malben, Beer Yakov, Israel.

endochondral ossification disorder, as described above, was there evidence of an inhibition of the longitudinal growth.

REPORT OF A CASE

I. E., born in Iraq, was a twenty-four year old male, whose father was suffering from pulmonary tuberculosis and diabetes mellitus. As a child, he had scarlet fever and pneumonia. No congenital changes had been observed. At the age of twenty-one, a specific lung process was discovered, and after a course of streptomycin in Iraq, the patient felt well. Two years after that, a relapse occurred while he was in Israel. Koch bacilli were found in his sputum and he was hospitalized. Upon admission to the hospital his general condition was poor; he was in a subfebrile state and had a sedimentation rate of 69 mm. (Westergreen).

Roentgenograms and laminagrams of the lungs revealed bilateral tuberculosis with a nut-sized infiltration below the right clavicle. The patient was treated with P.A.S. (1,300 gm. and rimifon (27.1 gm.), following which the lung condition improved and cultures of the laryngeal smear were repeatedly negative for tubercle bacilli.

Meanwhile, pains appeared in the back and in the right hypochondrium. A cold abscess was diagnosed and a puncture yielded 200 cc. of tuberculous pus. Roentgenograms at this time showed typical tuberculous spondylitis with destruction of D 12 and L 1. Operation was performed followed by antibiotics and P.A.S. therapy. The patient's condition improved steadily and the sedimentation rate went down from 70/120 mm. before the operation to 22/50 mm. four months after the surgical intervention, when he was transferred to a convalescent home, wearing an orthopedic belt.

Roentgen Findings. Apart from the above mentioned tuberculous spondylitis, roentgenographic study of the spine revealed severe osteoporosis of the vertebral column, with flattening of the vertebral bodies and formation of so-called fish-vertebrae. Furthermore, numerous areas of increased density were seen along the entire vertebral column, due to multiple spotty calcific deposits (Fig. 1–5). These deposits were located principally in the posterior parts of the vertebral bodies, between two fine, transverse lines of increased density which run parallel to the superior and inferior vertebral plates, thus representing lines of growth; in other words, the manifestation of a disorder in the growth of the vertebra. In the anteroposterior view, the numerous spotty calcific deposits were arranged in two symmetric lines, running vertically along the entire spinal column.

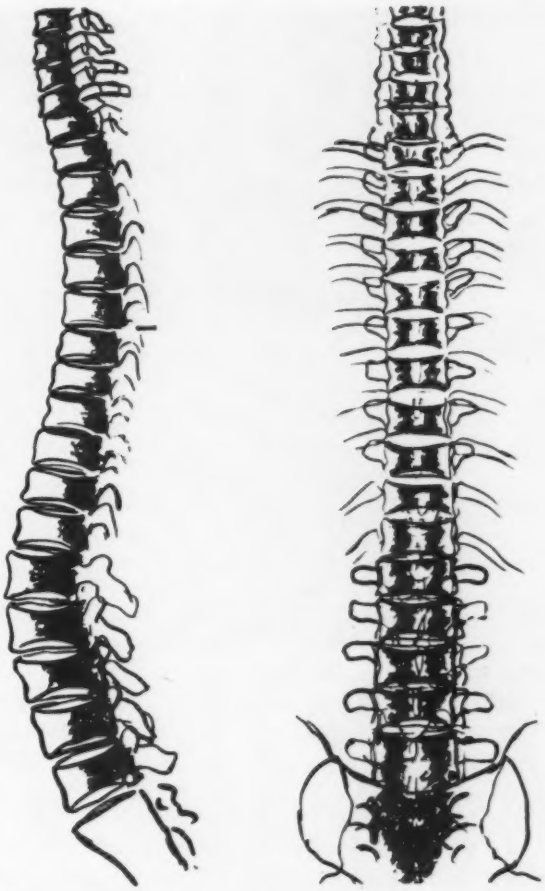


Fig. 1. Sketch of the entire vertebral column. The calcific densities in the lateral view are located in the posterior parts of the vertebral bodies; in the frontal view they appear as two parallel lines along the whole of the spine.

On the basis of the appearance in the lateral and anteroposterior roentgenograms it is assumed that the two groups of calcifications, located in the posterior parts of the vertebral bodies, lay opposite the two pedicles of the arches of the vertebrae (Fig. 6).

The patient also had a spina bifida of C 5 and C 6. Roentgenograms of the skull were negative. The blood chemistry and the basal metabolic rate gave normal values.

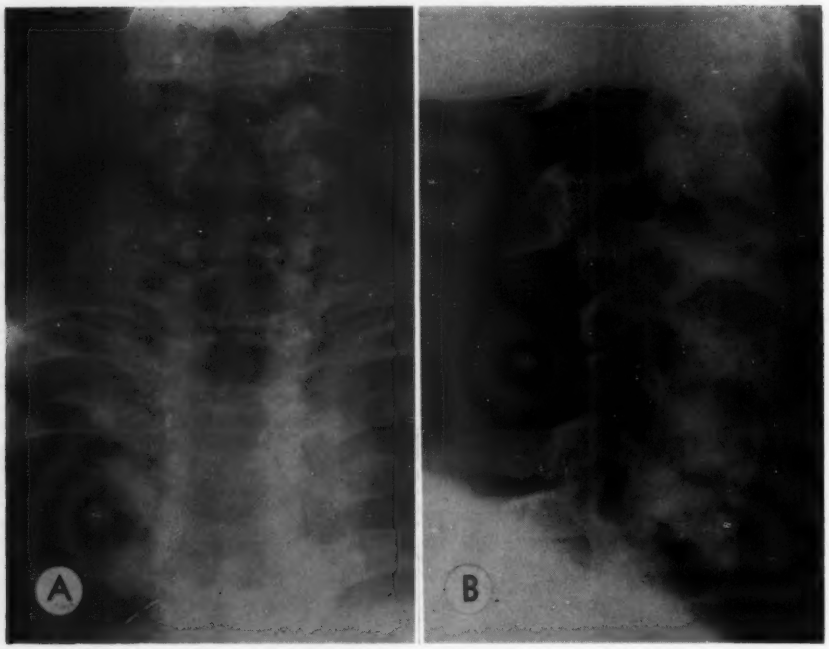


FIG. 2. Cervical vertebral column. In the anteroposterior roentgenogram (*A*) two symmetric lines of spotty calcific deposits are visible. In the lateral roentgenogram (*B*) these densities are situated in the posterior parts of the vertebral bodies. There is a spina bifida of C 5 and C 6.

DISCUSSION

In order to properly interpret the above described localization of the calcific deposits in the vertebra and to arrive at a correct diagnosis in this case, a brief review of the mode of ossification of the vertebra will prove useful. In fetal life, as well as after birth, each vertebra contains three ossification centers; one center in the vertebral body and two centers in the arch of the vertebra. The rest of the vertebra is cartilaginous and the width of the cartilaginous zone between the center of the vertebral body and the two centers of the arch of the vertebra depends on the stage of ossification (Fig. 7).

It is to be assumed that in our case the multiple, small, spotty calcific deposits came into existence in this cartilaginous part between the ossification center of the vertebral body and the two ossification centers of the arch of the vertebra, due to an otherwise unknown pathologic process in the prenatal stage (Fig. 8). Nevertheless, this case differs markedly from other cases of chondroangiopathia calcarea seu punctata in that the calcific deposits did not disappear during the first years of life, but are still visible in the entire vertebral column at the age of twenty-four. One might assume that, for some unknown reason, the pathologic process which led to the calcific deposits had not been completed and that the equally unknown factor of the disease continued to remain effective, thereby preventing the resorption of the calcific deposits during the first years of life. The transverse "lines of growth" also seem to point to continuation of the pathologic process in the region of the vertebral column after the synostosis of the vertebral arch with the vertebral body has occurred. These transverse "lines of growth" form a sort of frame, the borders of which are not traversed by the calcific deposits.

In the same way it might be assumed that the marked osteoporosis of the spine, with the characteristic flattening of the vertebrae, is due to the continued effect of the unknown factor of the disease after synos-

tosis of the vertebral arch with the vertebral body.

CONCLUSION

Regardless whether the hypothesis concerning the continuation of the unknown factor in chondroangiopathia calcarea seu punctata after completion of the synostosis and ossification of the vertebra is tenable, we can assume with some certainty that the case reported here represents an outstanding, atypical, stationary form of chondroangiopathia calcarea seu punctata that, so far, has not been described in the literature.

No changes were found roentgenologically outside of the spine, although it cannot be excluded that such changes might have been present during the first months after birth, disappearing later on, as seen in chondroangiopathia calcarea seu punctata. Should eventually cases be discovered in which the spine alone is affected, then one may speak of spondylochondroangiopathia calcarea seu punctata.

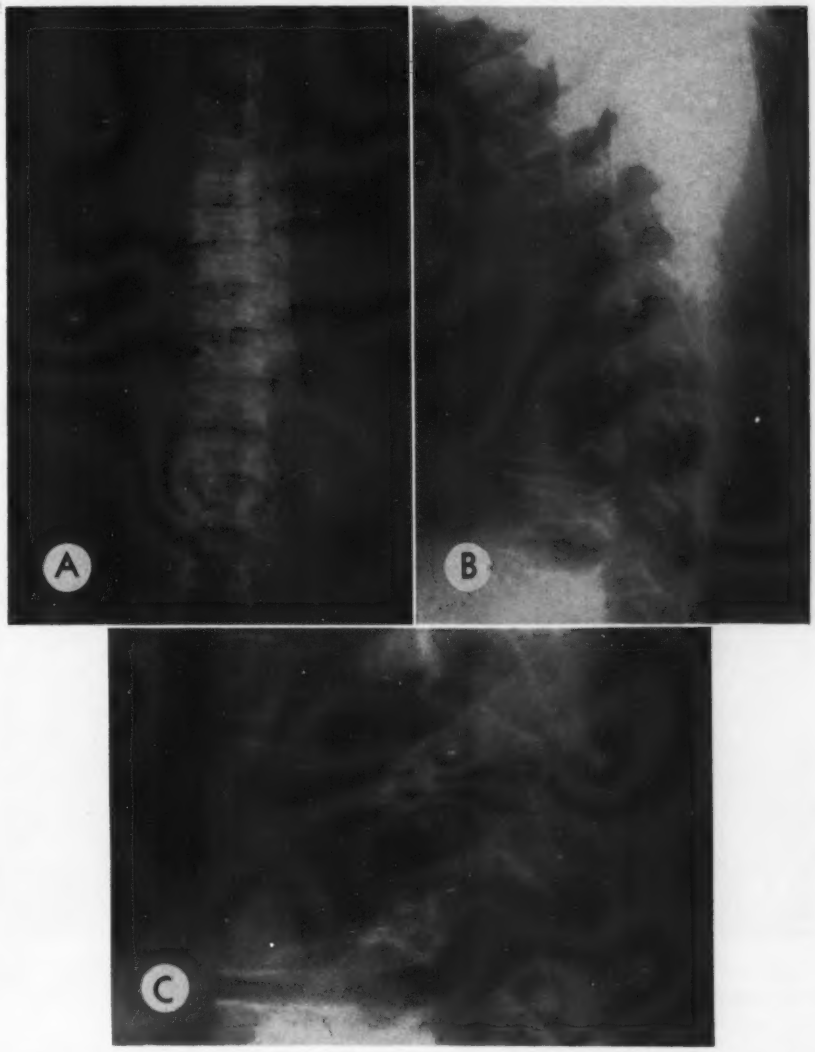


Fig. 3. Anteroposterior (*A*), lateral (*B*), and segmentally enlarged (*C*) roentgenograms of the thoracic vertebral column. Severe osteoporosis and flattening of the vertebrae, with the characteristic, localized, spotty calcific deposits between the clearly appearing transverse "lines of growth" in the vertebral bodies.

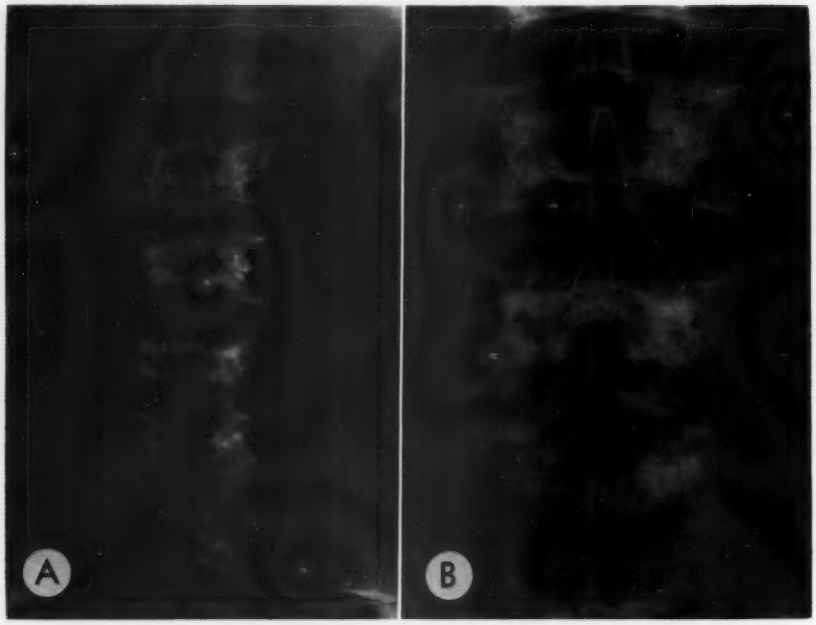


FIG. 4. Anteroposterior (*A*) and segmentally enlarged (*B*) roentgenogram of the lumbar vertebral column and sacrum. Flattening of the porotic vertebrae with two symmetric lines of spotty calcific deposits.

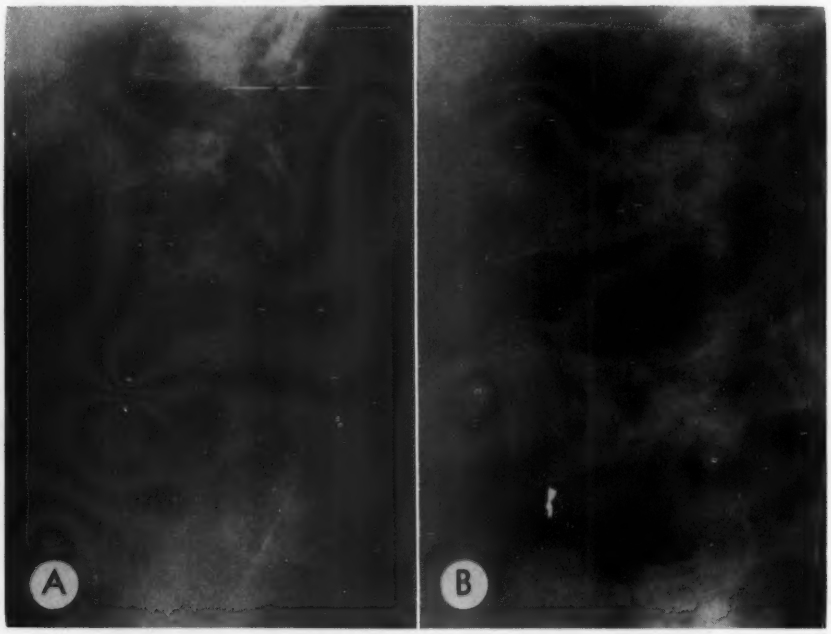


FIG. 5. Lateral (*A*) and segmentally enlarged (*B*) roentgenogram of the lumbar vertebral column. Flattening of the porotic vertebrae with densities in the posterior parts of the vertebral bodies.

Fig. 6. Sketch of an assumed cross-section through a lumbar vertebra. The two groups of calcific deposits most probably appear in the posterior parts of the vertebral bodies opposite the pedicles of the arch.

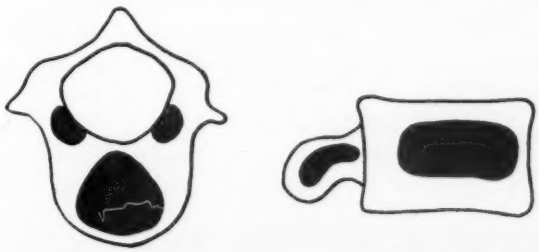


Fig. 7. Sketch of a vertebra in fetal life showing ossification from three centers; black—bone, white—cartilage.

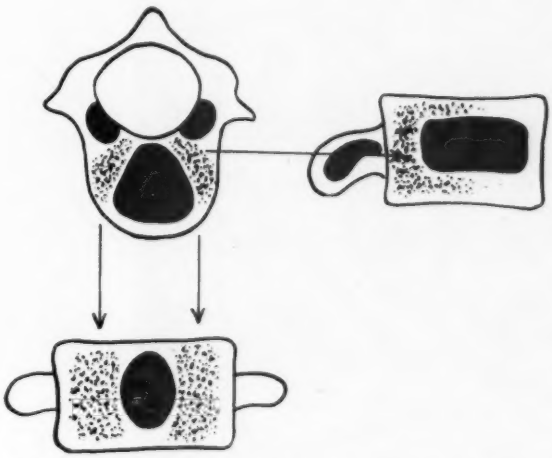


Fig. 8. Sketch of a vertebra in fetal life with the three ossification centers and with the possible calcific deposits; black—bone, white—cartilage, dotted—calcific deposits.

SUMMARY

The case of a twenty-four year old male patient has been described, in which roentgen study of the vertebral column for tuberculous spondylitis revealed the incidental findings of marked flattening of the vertebrae and multiple, small, spotty calcific deposits distributed along the entire spine. There was also evidence of transverse "lines of growth" in the vertebral bodies and the calcific deposits were located between these lines.

The case was considered to have an atypical, stationary and, so far, undescribed form of a rare congenital disease of infancy called chondroangiopathia calcarea seu punctata.

J. Licht, M.D.
86 Rothschild Blvd.
Tel-Aviv, Israel

REFERENCES

1. Bateman, D. Two cases and specimens from third case of punctate epiphyseal dysplasia. *Proc. Royal Soc. Med.*, 1935–1936, *29*, 745–746.
2. Borovsky, M. P., and Arendt, J. Chondrodystrophia calcificans congenita. *J. Pediat.*, 1944, *24*, 558–567.
3. Cocchi, U. Chondroangiopathia calcarea seu punctata. In Schinz, H. R., et al. Lehrbuch der Röntgendiagnostik. Band I. Georg Thieme Verlag, Stuttgart, 1950, 662–664.
4. Conradi, E. Vorzeitiges Auftreten von Knochen- und eigenartigen Verkalkungskernen bei Chondrodystrophia fötalis hypoplastica. Histologische und Röntgenuntersuchungen. *Jahr. f. Kinderh.*, 1914, *80*, 86–97.
5. Coughlin, E. J., Jr., Guare, H. T., and Moskowitz, A. J. Chondrodystrophia calcificans congenita; case report with autopsy findings. *J. Bone & Joint Surg.*, 1950, *32-A*, 938–942.
6. Fairbank, H. A. T. Dysplasia epiphysialis punctata. *J. Bone & Joint Surg.*, 1949, *31-B*, 114–122.
7. Geyman, M. J. Unusual manifestation of epiphyseal and joint pathology in new-born infant. Am. J. Roentgenol. & Rad. Therapy, 1931, *26*, 868–870.
8. Haynes, E. R., and Wangner, W. F. Chondroangiopathia calcarea seu punctata; review and case report. *Radiology*, 1951, *57*, 547–550.
9. Hilliard, C. Case of chondro-osseous dystrophy with punctate epiphyseal dysplasia. *Brit. J. Radiol.*, 1943, *16*, 144–146.

10. HÜNERMANN, C. Chondrodystrophia calcificans congenita als abortive Form der Chondrodystrophie. *Ztschr. f. Kinderh.*, 1931, *51*, 1–19.
11. JORUP, S. Fall von Chondrodystrophia congenita calcificans. *Acta radiol.*, 1944, *25*, 580–586.
12. LANG, F. J., and PRIESEL, R. Über chondrodysplasia (chondrodystrophia) calcificans congenita. *Forschungen u. Forscherg. der Tiroler Ärzteschule. Innsbruck*, 1947, 163.
13. MAITLAND, D. G. Punctate epiphyseal dysplasia occurring in two members of same family. *Brit. J. Radiol.*, 1939, *12*, 91–93.
14. MCCULLOUGH, J. A. L., and SUTHERLAND, C. G. Epiphyseal dysplasia puncticularis (stippled epiphyses) report of case not associated with hypothyroidism. *Radiology*, 1940, *34*, 131–135.
15. PAPARELLA-TRECCIA, R., and RAMPOLDI, A. La chondrodistrofia calcificante congenita. *Ortop. traumat. App. Mod.*, 1948, *16*, 75.
16. PAUL, L. W. Punctate epiphyseal dysplasia (chondrodystrophia calcificans congenita); report of case with nine year period of observation. AM. J. ROENTGENOL., RAD. THERAPY & NUCLEAR MED., 1954, *71*, 941–946.
17. RAAP, G. Chondrodystrophia calcificans congenita. AM. J. ROENTGENOL. & RAD. THERAPY, 1943, *49*, 77–82.
18. REILLY, W. A., and SMYTH, F. S. Stippled epiphyses with congenital hypothyroidism (cretinoid epiphyseal dysgenesis). AM. J. ROENTGENOL. & RAD. THERAPY, 1938, *40*, 675–681.
19. RESNIK, E. Epiphyseal dysplasia punctata in mother and identical male twins. *J. Bone & Joint Surg.*, 1943, *25*, 461–468.
20. SNOKE, P. O. Chondrodystrophia fetalis. AM. J. ROENTGENOL. & RAD. THERAPY, 1933, *29*, 31–42.
21. TISDALL, F. F., and ERB, I. H. Report of two cases with unusual calcareous deposits. *Am. J. Dis. Child.*, 1924, *27*, 28–38.
22. VINKE, T. H., and DUFFY, F. P. Chondrodystrophia calcificans congenita; report of two cases. *J. Bone & Joint Surg.*, 1947, *29*, 509–514.
23. WILKINS, L. Epiphyseal dysgenesis associated with hypothyroidism. *Am. J. Dis. Child.*, 1941, *61*, 13–34.

Vol. 78, No. 3

PREMATURE GROWTH ARREST OF THE KNEE EPIPHYSES

By DON E. MATTHIESEN, M.D.
PHOENIX, ARIZONA

GROWTH arrest at the level of the distal femoral or proximal tibial epiphyseal plate is not an uncommon occurrence in young people. However, the condition often is not discovered until clinical signs are fairly marked. Even then, patients are usually seen because of concern over cosmetic appearance rather than because of knee joint dysfunction.

There are certain early roentgen appearances which permit a diagnosis prior to clinical manifestations. It is well to be aware of these, inasmuch as growth disturbances in this region can cause marked deformities and functional disturbances about the whole lower extremity. Unequal leg lengths, genu varum and knock knee are all preventable deformities if the primary growth arrest of the epiphyseal plate can be detected in time.

Pathologically, the condition results from injury of the cartilaginous epiphyseal plate. Sometimes there may be crushing of a portion of the plate due to a fall from a height. Sometimes, due to faulty gait, the cartilage "wears" through at the point of greatest stress. This often follows upon hip joint disease, especially tuberculosis. Extreme decalcification is believed to be contributory, and in its presence, the possible development of growth arrest should be watched for.

Following the injury a bony bridge forms between the epiphysis and diaphysis at the site of cartilage interruption. It is this formation which causes the distinctive roentgenographic appearance; and the longer the injury has been present, the more pronounced are the findings.

Certain sites seem to be favored. In the

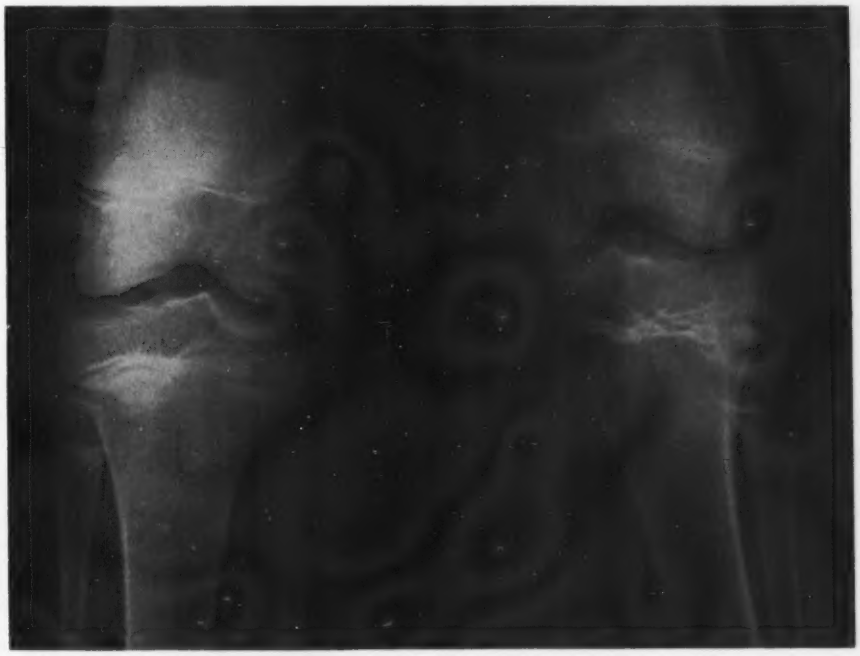


FIG. 1. Changes secondary to tibial bowing. Stellate appearance created by converging striations, underdeveloped intercondylar spine, flattening of tibial epiphyseal plate and deepening of intercondylar notch of femur. There is also premature fusion of distal femoral epiphysis and moderate genu valgum.

Fig. 2. Lateral projection again demonstrates radiating striations as well as maldevelopment of tibial tubercle.

posterior medial quadrant of the proximal tibial plate, there is a relatively high incidence of such developments. In the distal femur the premature fusion across the epiphyseal plate is likely to be just posterior to the central part of the disk. The tibial tubercle also often unites prematurely with its metaphysis.

Early roentgenographic changes are thinning of the disk of epiphyseal cartilage and the presence of a transverse zone of dense bone on its metaphyseal side. Bony striations crossing the central portion of the cartilage plate may be the earliest roentgenographic indication of such union. Later, growth retardation scars, trabeculae which converge toward the site of the bony bridge from epiphysis and metaphysis, are seen to develop. These evidently develop as a result of continued growth of uninvolved portions of the plate, and a stellate or sunburst appearance is created by the radiating striations. Histologically, transversely oriented trabeculae can be seen covering the metaphyseal surface of the plate.

The line of epiphyseal union may become bent, forming an inverted V in the distal femur or a deepening of the intercondylar notch. In the proximal tibia the epiphyseal line is too flat or even cupped upward. The tibial spine is underdeveloped. The tibial tubercle may be misshapen. If the initial bony bridge is eccentrically situated, there may be valgus or varus deformity at the knee joint.

The contour of the epiphyseal cartilage is irregular with peaks projecting into the metaphysis. It is thought that some of these may become detached to form cartilaginous rests which come to lie deeper within the metaphysis during the normal course of growth. Radiolucencies in the metaphysis which have been described as cortical defects are not infrequently seen in association, and may signify deranged endochondral bone formation. Regional demineralization may be observed.

The stellate roentgenographic appearance described is almost certain evidence of growth arrest of part of the epiphyseal plate, and careful examination will usually show other evidences of premature fusion. Certainly, comparison with roentgenograms of the normal side is indicated.

There is no way to produce normal growth from an epiphyseal plate which has undergone partial or complete fusion. If asymmetry is beginning to develop, surgical epiphyseal arrest will probably be necessary to equalize leg lengths and to prevent alignment abnormalities. In routine examinations of the knee joints in young people, familiarity with the signs of growth arrest will permit early recognition and institution of treatment when it is likely to be least disruptive.

926 E. McDowell Road
Phoenix, Arizona

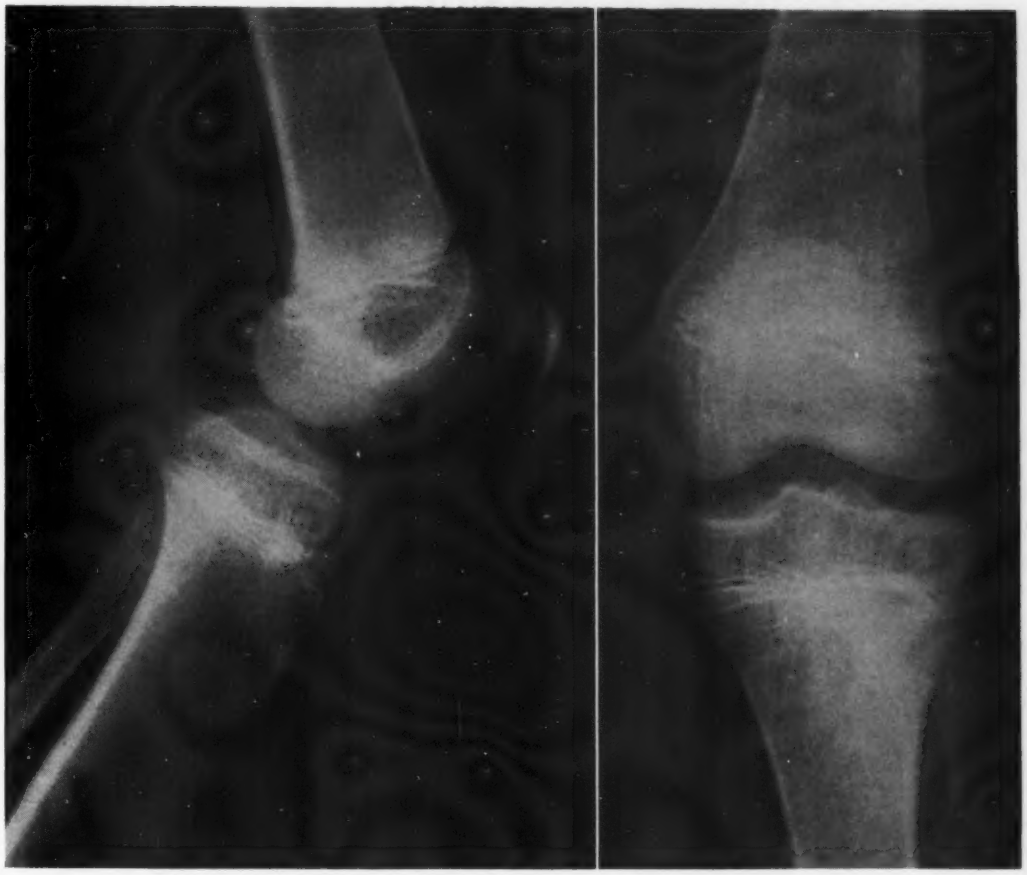


Fig. 3. An earlier case illustrating flattening and slight bone thickening adjacent to medial portion of tibial epiphyseal plate, with striations crossing the same area vertically.

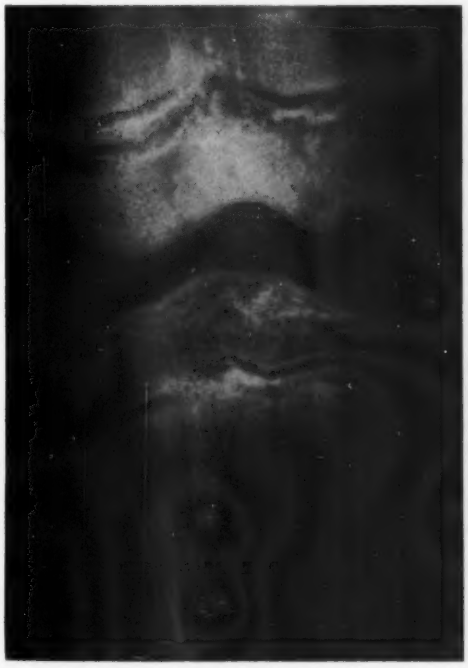


Fig. 4. Premature growth arrest in proximal tibia and distal femur associated with deranged endochondral bone formation. The inverted V shape of distal femoral epiphyseal plate is well shown.

REFERENCES

1. Abbott, L. C., and Gill, G. G. Valgus deformity of knee resulting from injury to lower femoral epiphysis. *J. Bone & Joint Surg.*, 1942, *24*, 97–113.
2. Gill, G. G. Cause of discrepancy in length of limbs following tuberculosis of hip in children. *J. Bone & Joint Surg.*, 1944, *26* 272–281.
3. Lindsay, D. T. Foot problems in children. *Postgrad. Med.*, 1952, *12*, 177–180.
4. Ross, D. Disturbance of longitudinal growth associated with prolonged disability of lower extremity. *J. Bone & Joint Surg.*, 1948, *30-A*, 103–115.

EOSINOPHILIC GRANULOMA OF BONE

By J. GEORGE TEPLICK, M.D.,* *and* HAROLD BRODER, M.D.†
PHILADELPHIA, PENNSYLVANIA

EOSINOPHILIC granuloma of bone was introduced as a distinct clinical and pathologic entity in 1940 through the publications of Lichtenstein and Jaffe,[10] and Otani and Ehrlich.[15] By 1953, approximately 200 cases had been reported. The following case of eosinophilic granuloma has several unique and interesting features which warrant its publication and discussion.

REPORT OF A CASE

E.S., a sixty-two year old white female, had been under treatment at The Kensington Hospital diabetes clinic. In November, 1954, she first complained of discomfort in the right shoulder area. Roentgenograms on November 8, 1954 (Fig. 1), disclosed peculiar changes in the form of small radiolucent areas parallel to the outer border of the acromion and an irregular linear plaque of amorphous calcification in the adjacent soft tissues. The surrounding soft tissues appeared somewhat thickened. There was no history of previous trauma, infection or difficulty involving the right shoulder.

She was hospitalized on November 18, 1954, because of increasing difficulty in controlling her diabetes and progressive discomfort and loss of motion in the right shoulder. Physical examination at that time revealed an elderly woman, rather poorly nourished who was in no acute distress. Tenderness was found over the edge of the acromion and the overlying soft tissues were thickened, edematous, and slightly warmer than normal. Shoulder motion was moderately restricted in all directions. The remaining physical findings were within normal limits. The temperature, pulse and respiration were consistently normal.

Laboratory studies disclosed a blood sugar of 314 mg. per cent, sugar in the urine, a mild anemia (9.3 gm. hemoglobin) and a normal white blood cell count. During the twelve day hospital stay, her diabetes was brought under control. Hydrocortisone was injected into the shoulder with considerable relief.

FIG. 1. November 8, 1954. Peculiar changes in acromial tip. The calcification in the soft tissues may represent detached bone fragments. Note soft tissue swelling.

After discharge from the hospital, the shoulder pain and swelling became increasingly more severe. She was re-admitted to Kensington Hospital on December 16, 1954. Roentgenographic study of the shoulder on this date (Fig. 2), five weeks after the original, revealed marked changes. There was extensive irregular destruction of both the edge of the acromion and the outer end of the clavicle. Many ragged bony edges were seen which appeared to merge with the soft tissue calcification previously noted. Considerable soft tissue swelling was apparent. Since primary bone tumors rarely cross cartilaginous joints, a soft tissue malignant neoplasm with secondary involvement of the acromion and clavicle was suspected. Roentgen survey of the chest, pelvis and spine revealed no other bone lesions. Laboratory studies were again noncontributory. A mild anemia was again noted.

On December 16, 1954, surgical exploration was undertaken. The skin and soft tissues overlying the right shoulder were edematous. On splitting the muscle fibers of the deltoid, yel-

* Department of Radiology, Kensington Hospital, Philadelphia, Pennsylvania.
† Department of Orthopedic Surgery, Kensington Hospital, Philadelphia, Pennsylvania.

lowish-gray-red myxomatous type of tissue was found in the subdeltoid bursa. This same tissue had eroded and replaced the destroyed portions of the acromion, acromioclavicular joint and the adjacent clavicle. The rotator cuff was swollen, but uninvolved. No pus was encountered. Ample portions of the tumor tissue and bone were removed for microscopic examination.

The pathologic report by Dr. R. M. Shuffstall stated that microscopically the fragments consisted largely of rather large mononuclear cells with an accompanying fibrous stroma and numerous small proliferating blood vessels. Also present were occasional multinucleated giant cells, presumably resulting from fusion of the previously described mononuclear cells, and quite conspicuous areas of eosinophilic leukocytes. Spicules of bone present showed both osteolytic and osteoblastic activity and there were a few small foci of intense polymorphonuclear leukocytic exudation. Diagnosis: Eosinophilic granuloma of soft tissues, acromion and clavicle (Fig. 5). Because of the unexpected findings, the slides were evaluated by a number of other pathologists, with unanimous concurrence of the diagnosis of eosinophilic granuloma.

The patient recovered uneventfully from the surgical procedure and left the hospital four days later. In early January, 1955, a course of deep roentgen therapy was instituted. Treatment was administered with 200 kv. peak, at 50 cm., with 0.5 mm. Cu filtration. A 15 cm. circular port was directed to the involved area, and 200 r in air was given daily, for a total dose of 2,000 r in air, with a calculated tumor dose of nearly 1,800 r. The response to the irradiation was prompt and gratifying. Within two weeks after initiating therapy, the pain was completely abolished, and increased motion of the shoulder was apparent. The soft tissue swelling disappeared completely within one month. Roentgenograms made a month (February 19, 1955) after initiating therapy (Fig. 3) revealed considerable reconstitution of the acromion and outer clavicle. The soft tissues were no longer thickened. Examination again on March 31, 1955 (Fig. 4) indicated almost complete restoration of the acromion, with considerable trabecular irregularity remaining. The outer clavicle appeared practically normal. In September, 1955, she was free of pain or disability in the right shoulder. Later roentgenograms revealed little or no change since the films of March 31, 1955. No clinical or roentgen evidence of new lesions has been uncovered.

Fig. 2. December 16, 1954. Marked destruction of acromion and outer end of the clavicle.

Fig. 3. February 9, 1955. One month after beginning roentgen therapy. Roentgenogram shows considerable regeneration of acromion and clavicle.

DISCUSSION

Eosinophilic granuloma of bone occurs most frequently in children or young adults. About 5 per cent are found in persons over thirty years of age.[4] Over 60 per cent occur in individuals under the age of twenty. Fetal involvement has been reported in 1 instance.[5] Occasional reports of

FIG. 4. March 31, 1955. There is now practically complete restoration of the clavicle and the acromion is healed, with residual trabecular deformity.

eosinophilic granuloma in patients fifty years old have appeared.[4,16,21] The patient presented here (aged sixty-two) is apparently the oldest individual to develop this granuloma. No significant sex predilection has been established.

Like most bone tumors, eosinophilic granuloma is of unknown etiology. Trauma has been implicated as a predisposing factor,[2,19,23] but no clearcut relationship can be established.

Clinically, the afflicted individual is most often a child or young adult, with a history of pain and some soft tissue swelling over the involved bone or bones. Localized tenderness can usually be elicited. Distinct soft-tissue masses may appear over the involved area. Overlying muscles may show spasm or even some atrophy. Mild systemic disturbances of slight fever, malaise and anorexia may be present. Slight leukocytosis with some increase in eosinophils and an increased sedimentation rate occur in some cases. The symptoms, especially the pain, are slowly progressive. There may be a lapse of many months from the clinical onset until medical advice is sought.

The osseous lesions are usually solitary (75 per cent of cases) and most commonly involve the skull, ribs or femora (59 per cent).[4] However, as increasing numbers of cases are reported, practically every bone has been implicated. The lesions apparently originate in the medullary portion of the bone.

Extra-osseous lesions of eosinophilic granuloma are uncommon. McCullough[14] described a case with multiple bone lesions and soft tissue granulomata in the gingiva, perineum and anus. A diaphragmatic eosinophilic granuloma was reported by Ackerman.[1] Pulmonary lesions have also been described.[1,3,6,16] These may be miliary or localized. Even skin lesions with ulceration have been reported.[13]

Since the first description of eosinophilic granuloma, intense speculation has arisen concerning its relationship to Hand-Schüller-Christian disease and to Letterer-Siwe disease. Most authors consider all three conditions to be related reticulogranulomas, and accept the Pinkus classification of 1949, in which four types are distinguished:

1. A systemic type with an acute clinical course, which is usually fatal. This is a nonlipoid reticulosis. It occurs exclusively in children two to three years old, with hepatosplenomegaly, adenopathy, 2° anemia and hemorrhagic diathesis (Letterer-Siwe disease).

2. The granulomatous type, with a chronic and progressive clinical course. Xanthomatous transformation of the granulomata dominates the histologic picture

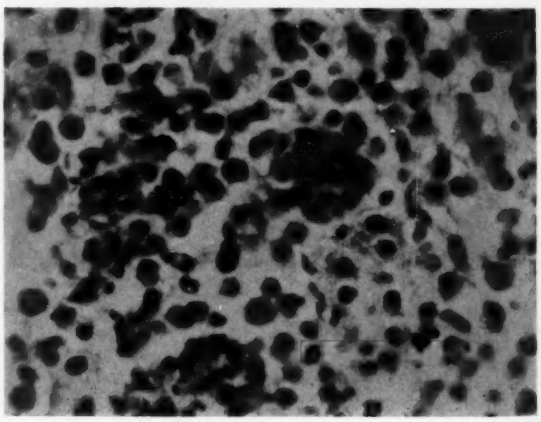


FIG. 5. Photomicrograph of soft tissues, showing typical picture of eosinophilic granuloma.

(Hand-Schüller-Christian disease). The classic triad of cranial bone defects, exophthalmos and diabetes insipidus is not constant. Various symptoms can appear, depending on the location and extent of the granulomatous lesions.

3. The benign form is usually localized to bones (osteolytic lesions) with definite tendency to spontaneous healing (eosinophilic granuloma). This form appears in late childhood and early adult life.

4. Mixed type.

Numerous striking cases have appeared in the literature in which transition occurs,[1,7,9,11,14,16,18] especially from eosinophilic granuloma to xanthomatous Hand-Schüller-Christian disease. Hansen[7] believes that the histopathology is clearly indicative of continuous transition, and lists 4 distinct histologic phases:

1. The hyperplastic, proliferative reticulohistiocytic phase, which is acute and malignant. This picture features Letterer-Siwe disease.

2. The granulomatous phase, with eosinophils, macrophages and giant cells. This is typical of eosinophilic granuloma.

3. Infiltration of the granuloma by lipoid storage (foam) cells. This foam cell overgrowth is characteristic of Hand-Schüller-Christian disease.

4. Fibrous healing, of Phase 2 or 3. Thus, Hansen considers all phases as part of the same disease, a reticuloendothelial disorder.

Agreement on the relationship of the 3 conditions is well nigh unanimous, albeit not all writers agree on the transition of one into the other. Henderson, Dahlin and Bickel[8] find insufficient evidence to support the belief that eosinophilic granuloma is an early stage or phase of Hand-Schüller-Christian disease. They will diagnose eosinophilic granuloma only if no visceral lesions are evident, and if no more than 2 bone lesions are uncovered. If one or more of the classic triad appears (exophtalmos, diabetes insipidus and multiple skull lesions) or if visceral lesions exist, these authors consider the diagnosis to be Hand-Schüller-Christian disease. The absence of foam cells, however, does not rule out Hand-Schüller-Christian disease.

The histopathology of eosinophilic granuloma, already briefly described above, consists of a fibrous stroma, within which are mono and multinuclear histiocytes and giant cells with foci of eosinophils. An occasional foam cell does not invalidate the diagnosis of eosinophilic granuloma in the opinion of most pathologists. Walthard and Zuppinger[22] list 12 histologic points in the microscopic diagnosis of eosinophilic granuloma: (1) reticular groundwork; (2) eosinophils; (3) giant cells, 2–30 nuclei and phagocytosis; (4) macrophages with nuclear fragments, eosinophils and hemosiderin; (5) massive numbers of lymphocytes, plasma cells and neutrophils; (6) small necrotic foci; (7) foci of hemorrhage; (8) numerous vessels, often thick-walled; (9) bone destruction with sequestration, periosteal bone formation and osteogenic reaction with osteoclasts; (10) Charcot-Leyden crystals; (11) occasional foam cells with neutral fat; (12) transition from granulation to connective tissue in direction of healing.

The roentgen appearance of bone alterations in eosinophilic granuloma generally consists of round, oval or irregularly shaped areas of decreased density which usually are sharply demarcated from the surrounding bone. The size in most reported cases varies from 1 to 5 cm. in diameter. Rarely, marginal sclerosis is found. Periosteal thickening may occur with lesions in the long bones. A bone sequestrum within the area of destruction has been described by Wilson, Minteer and Hayes.[23] In Hand-Schüller-Christian disease, the bone lesions have the same roentgen appearance.

The most commonly affected sites are the skull, ribs and femora, although practically every bone may be involved, including the phalanges.[12] Involvement of the scapula and clavicle, however, is rare. The lesions progress quite slowly, although Baker *et al.*[2] report rapid progression within one month. The present case, too, showed star-

tling progression one month after discovery. The bone lesions of eosinophilic granuloma have a distinct tendency towards healing, although complete spontaneous recovery is infrequent. The condition is benign, and no fatalities are to be expected unless transition to Hand-Schüller-Christian disease occurs. Serious disability is uncommon, but depends upon the anatomic area involved, and, of course, the extent of the bone involvement. Treatment is usually quite satisfactory. After biopsy has determined the diagnosis, lesions which are easily accessible may be curetted or excised, with a high percentage of permanent cures.[4] Irradiation is very effective, leading to both bone and soft tissue recovery. The technique of irradiation is relatively simple. Utilizing 200–240 kv. peak, a total dose of 700–2,000 r (in air) will generally prove sufficient. The excellent results from irradiation are to be found in many of the case reports.[4,8,14,17,20] The roentgen therapy is accepted as a preferred method of treatment by most of the authors on this subject. Dickson[3] treated the lungs of one patient with pulmonary infiltration, but without appreciable change of the roentgen appearance.

CASE DISCUSSION

From the above data on eosinophilic granuloma, it is apparent that the case presented here is a unique one. The age at onset (the time of onset could easily be pinpointed from the clinical symptoms and the early roentgenographic changes) was sixty-two years. Apparently, this is the oldest reported individual to develop eosinophilic granuloma. The middle fifties was the oldest in the literature.[4,16,21]

The early roentgen appearance was quite atypical. No clearcut bone defect was seen; soft-tissue calcification adjacent to the acromion and irregularity of the lateral tip of the acromion with spotty areas of demineralization were the roentgen findings (Fig. 1). Soft tissue swelling (typical) was also noted. The rapid progression of the bone lesion and the unexpected involvement of an adjacent bone (clavicle, outer end; Fig. 2) are features of unusual interest. Only five weeks intervened between the two film studies.

The clinical features of progressive pain and disability and of soft tissue swelling in the shoulder are fairly typical of eosinophilic granuloma. No systemic complaints or significant laboratory findings appear to have resulted from the local involvement. The diabetes mellitus was obviously unrelated, antedating the bone lesion by many years.

The histology of the bone lesion (see case report) was quite typical of eosinophilic granuloma; no lipophages or foam cells were seen. The rigid criteria of Henderson, Dahlin and Bickel[8] are fulfilled in this case; *viz.*, not more than 2 bones were involved, and no foam cells were found histologically.

Therapeutically, a highly satisfactory result was achieved by roentgen irradiation. Although a total of 2,000 r (in air) was given, clinical improvement became quite apparent after about 800 r. Figure 4 demonstrates the remarkable restoration of bone and soft tissue contours two months after therapy was completed. The calculated tumor dose was nearly 1,800 r.

SUMMARY

1. An unusual case of eosinophilic granuloma in a sixty-two year old woman is reported. Apparently, she is the only known individual to develop this condition so late in life.

2. Other unique features included atypical early roentgenographic findings, unusually rapid progression, and extension of the lesion across the acromioclavicular joint to involve the clavicle.

3. Even at this age, roentgen therapy produced an excellent result, with marked clinical and roentgenologic improvement.

4. Discussion of the salient features of eosinophilic granuloma is included, together with a brief review of the relationship to

Hand-Schüller-Christian disease and to Letterer-Siwe disease.

J. George Teplick, M.D.
Kensington Hospital
Philadelphia, Pennsylvania

REFERENCES

1. Ackerman, A. J. Eosinophilic granuloma of bones associated with involvement of lungs and diaphragm. Am. J. Roentgenol. & Rad. Therapy, 1947, *58*, 733–740.
2. Baker, W. J., Houghton, J. D., Wissing, E., and Betts, R. H. Eosinophilic granuloma; report of case with x-ray evidence of rapid progression. *New England J. Med.*, 1948, *238*, 626–629.
3. Dickson, D. D. Eosinophilic granuloma of bone with diffuse pulmonary involvement. *California Med.*, 1948, *69*, 51–53.
4. Dundon, C. C., Williams, H. A., and Laipply, T. C. Eosinophilic granuloma of bone. *Radiology*, 1946, *47*, 433–444.
5. Garsche, R. Über eine connatale Knochenerkrankung unter dem Erscheinungsbild eines atypischen eosinophilen Granuloms. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1953, *78*, 63–70.
6. Gilbert, R., and Voluter, G. Morphologie radiologique pulmonaire d'un granulome histiocyte-éosinophile de la machoire inférieure et de la calotte cranienne. *J. de radiol. et d'électrol.*, 1947, *28*, 465–467.
7. Hansen, P. B. Hand-Schüller-Christian's disease, Letterer-Siwe's disease and eosinophilic granuloma of bone (with report of 5 cases). *Acta radiol.*, 1949, *32*, 98–112.
8. Henderson, E. D., Dahlin, D. C., and Bickel, W. H. Eosinophilic granuloma of bone. *Proc. Staff Meet., Mayo Clin.*, 1950, *25*, 534–541.
9. Lichtenstein, L. Histiocytosis X; integration of eosinophilic granuloma of bone, "Letterer-Siwe disease," and "Schüller-Christian disease as related manifestations of single nosologic entity. *A.M.A. Arch. Path.*, 1953, *56*, 84–102.
10. Lichtenstein, L., and Jaffe, H. L. Eosinophilic granuloma of bone, with report of case. *Am. J. Path.*, 1940, *16*, 595–604.
11. Li Moli, S. Malattia di Hand-Schüller-Christian con reperto istologico de granuloma eosinofilo. *Riv. clin. pediat.*, 1953, *51*, 641–657.
12. Loehr, W. M. Eosinophilic granuloma of bone in hand. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1957, *47*, 568–570.
13. McCreary, J. H. Eosinophilic granuloma with simultaneous involvement of skin and bones. *Arch. Dermat. & Syph.*, 1947, *59*, 372–380.
14. McCullough, N. B. Eosinophilic granuloma with multiple osseous and soft-tissue lesions in adult. *A.M.A. Arch. Int. Med.*, 1951, *88*, 243–251.
15. Otani, S., and Ehrlich, J. C. Solitary granuloma of bone simulating primary neoplasm. *Am. J. Path.*, 1940, *16*, 479–490.
16. Parkinson, T. Eosinophilic xanthomatous granuloma with honeycomb lungs. *Brit. M. J.*, 1949, *1*, 1029–1030.
17. Platt, J. L., and Eisenberg, R. B. Eosinophilic granuloma of bone; report of 6 cases. *J. Bone & Joint Surg.*, 1948, *30-A*, 761–768.
18. Ponseti, I. Bone lesions in eosinophilic granuloma, Hand-Schüller-Christian disease and Letterer-Siwe disease. *J. Bone & Joint Surg.*, 1948, *30-A*, 811–833.
19. Ramioul, H., Gomez, J., and Damiean-Gillet. Granulome éosinophile de l'os (étude d'un cas). *Acta chir. belg.*, 1950, *49*, 626–633.
21. Versiani, O., Figueiro, J. M., and Junqueira, M. A. Hand-Schüller-Christian's syndrome and "eosinophilic or solitary granuloma of bone. *Am. J. M. Sc.*, 1944, *207*, 161–166.
22. Walthard, B., and Zuppinger, A. Das eosinophile Granulom des Knochens. *Schweiz. med. Wchnschr.*, 1949, *79*, 618–623.
23. Wilson, R. G., Minteer, D. W., and Hayes, J. D. Report of case of eosinophilic granuloma of bone with roentgenographic demonstration of sequestrum. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1953, *69*, 936–939.

CONGENITAL SUPERIOR ECTOPIA OF THE KIDNEY*

By HERBERT S. BERLIN, M.D.,† JOSEPH STEIN, M.D.,‡ *and* MAXWELL H. POPPEL, M.D.§
BRONX, NEW YORK

THE preoperative identification of a mass discovered on the chest roentgenogram poses a challenge for diagnosis of more than academic importance. This report describes instances of varying degrees of high ectopia of the left kidney (and possibly the adrenal) in 2 patients and bilaterally superiorly placed kidneys in a third patient, presenting on the chest roentgenogram as lobular masses, that were identified by urography. In 1 patient treated earlier for two separate malignant neoplasms, the positive identification of the mass at the base of the left lung altered what would have been a seemingly "hopeless prognosis" and possibly unnecessary operation. In the second, an asymptomatic employee of the hospital, the roentgenographic diagnosis, likewise, eliminated much personal concern and doubt and unnecessary diagnostic procedures. In the third patient, the findings were discovered incidentally. There was no evidence of trauma in these cases and the abnormalities observed are presumed to be solitary and congenital in basis and are added to 10 similar published cases diagnosed roentgenographically which vary primarily in the height of the superior ectopia. The third case, however, with bilateral changes, is apparently unique.

REPORT OF CASES

CASE 1. A sixty-two year old male has been followed at the Bronx Veterans Administration Hospital since 1940, when he had been admitted for the excision of a recurrent tumor of the anterior abdominal wall, the site of several previous local excisions. In 1922, the patient had first noted just above his umbilicus a small lump which was removed and reported as neurofibroma of the anterior abdominal wall. In 1924, and again in 1938 and 1939, progressively larger sized local reccurrences required repeated excisions. In 1939, biopsy revealed fibrosarcoma and he was referred to the Veterans Administration Hospital. During the next fifteen years, the patient returned 8 times for excisions of locally recurring tumor masses, which were all interpreted histologically as dermato-fibrosarcoma of the anterior abdominal wall.

On his last visit in May, 1954, a needle biopsy of a nodular prostatic enlargment disclosed adenocarcinoma. This was first treated by stilbesterol, and subsequently by a bilateral orchiectomy.

During the entire period of observation, the patient had never experienced any symptom that might have suggested metastatic disease and skeletal surveys and serum phosphatase determinations have been normal.

A "well defined homogeneous density overlying the left dome of the diaphragm" was noted on a chest roentgenogram dated December, 1942. This finding aroused concern, especially after the pathology report of dermatofibrosarcoma, but was not noted by several subsequent observers. It was again appreciated and described as being larger prior to the discovery of the patient's second malignancy (probably related to phase of respiration and positioning of the patient). The radiologist suggested the possibility of kidney herniation because of the shape and locale of the lobular mass on the plain roentgenograms of the chest dated May, 1955 (Fig. 1). An intravenous pyelogram obtained, coincidentally, to evaluate the status of the renal collecting systems, however, was interpreted only as demonstrating "renal clearance with details obscured by excessive gas and soft tissue shadows." (The positioning of the patient, in the usual manner, did not include

* From the Radiological Service, Veterans Administration Hospital, Bronx, New York.
† Formerly, Associate Radiologist, Veterans Administration Hospital, Bronx, New York.
‡ Chief, Radiology, Veterans Administration Hospital, Bronx, New York and Assistant Clinical Professor, Radiology, New York University College of Medicine.
§ Professor and Chairman of Radiology, New York University College of Medicine and Consultant, Radiology, Veterans Administration Hospital, Bronx, New York.

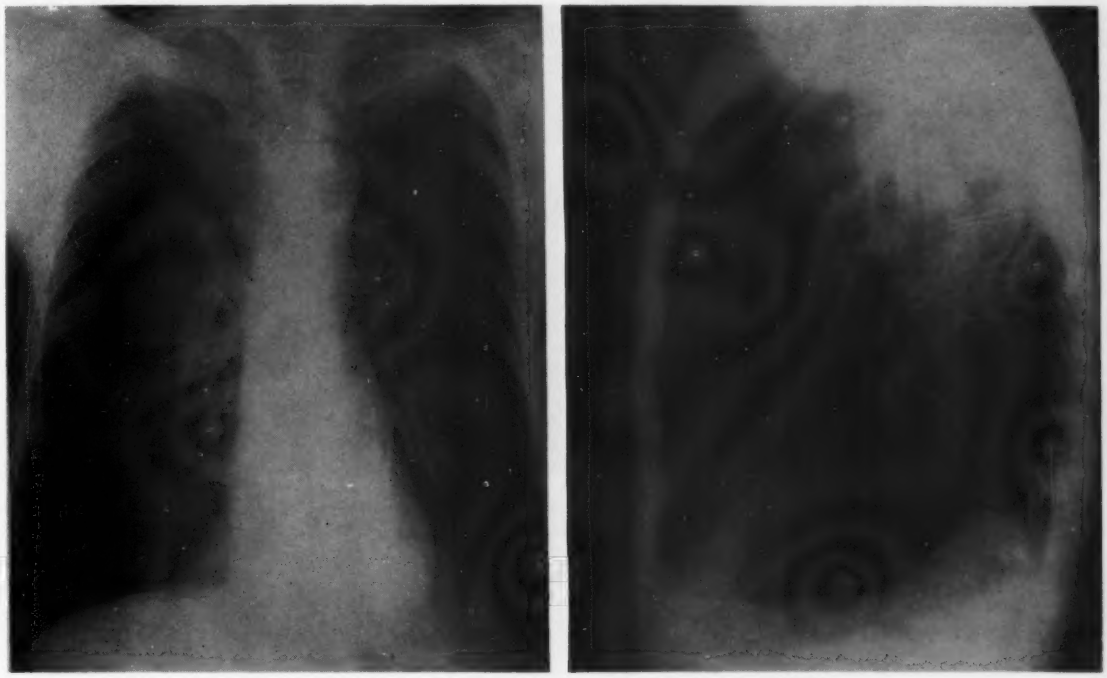


Fig. 1. Roentgenograms of the chest of the first case disclose the abnormal reniform "mass" at the left base, posteriorly.

Fig. 2. Intravenous pyelogram, obtained with appropriate positioning of the patient, identifies the ectopic left kidney and its relationship to the diaphragm. A soft tissue density eccentrically capping the superior pole of the ectopic kidney may represent the left adrenal gland or perinephric soft tissues. Renal clearance and the calyceal structures appear normal. Note, however, the elongated left ureter and the abnormal renal axis.

visualization of the diaphragmatic leaflets.)

The abnormal finding was again noted on a photoroentgen examination of the chest three months later. The diagnosis of left renal ectopy was established upon review of the previous excretory pyelogram, and anticipating the anomaly a repeat examination was arranged, with the patient appropriately positioned to allow visualization of the lower one-third of the thorax (Fig. 2). Fluoroscopically, the left diaphragmatic motion lagged and the bulge appeared to move minimally, and paradoxically. There was no history of trauma and the anomaly was presumed to be congenital.

Case II. A thirty-four year old asymptomatic male employee was found to have a lobular density at the posterior left lung base in 1954 (Fig. 3). Fluoroscopically, the density appeared relatively fixed in position and normal diaphragmatic motion on this side was restricted (Fig. 4). There was no history of trauma.

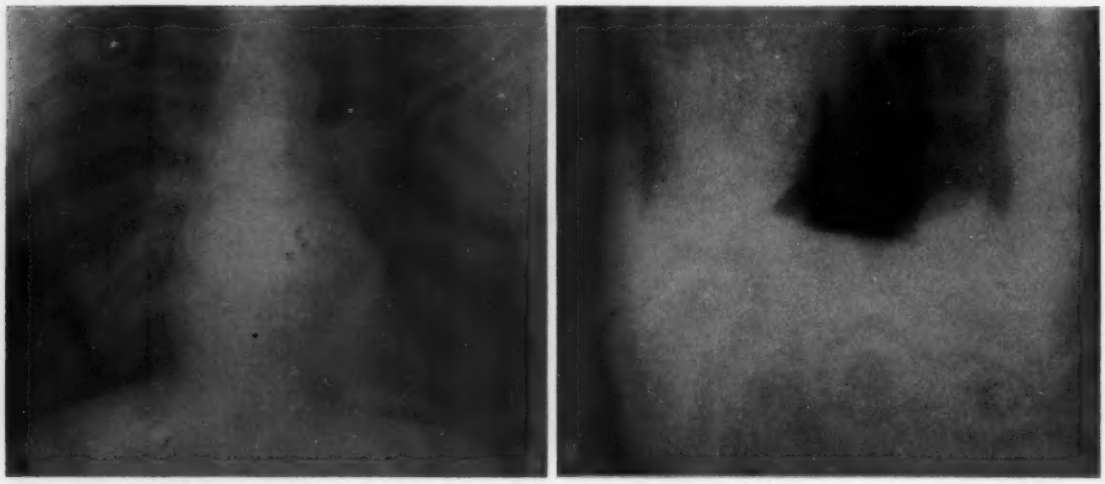


FIG. 3. Chest roentgenogram of Case II demonstrates the lobular mass projecting above the left diaphragmatic leaflet, behind the cardiac shadow (*A*), seen to better advantage on the lateral laminagram (*B*).

The reniform shape and locale of the density suggested ectopy of the kidney which was confirmed on subsequent pyelographic studies (Fig. 5). Laminagrams demonstrated a faint lucent plane at its upper pole, possibly the inferior border of the suprarenal gland which may be associated with the superior ectopy of the left kidney (Fig. 3*B*).

CASE III. A sixty-one year old male was transferred to the Bronx Veterans Administration Hospital after bronchoscopy was reported abnormal at another Veterans Administration installation. The patient had complaints associated with chronic cardiopulmonary disease and peripheral arteriosclerosis. He had sustained no previous trauma.

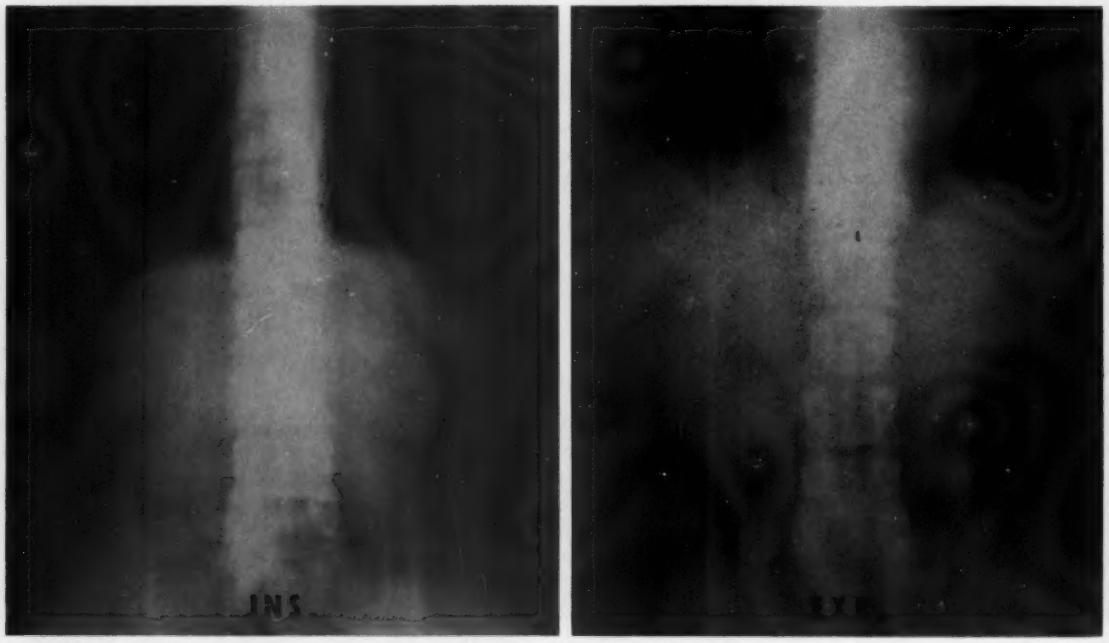


FIG. 4. Roentgenograms taken during the phases of respiration demonstrate the relative fixation of the mass, and a slight restriction to the excursion of the otherwise normal appearing left diaphragmatic leaflet.

Early roentgenograms demonstrated a focalized zone of honeycombed changes and abnormal markings in the parenchyma of the right lower lobe of the lung. The diaphragmatic leaflets were described as being "mammilated." During the roentgenographic follow up, the pulmonary changes were observed to clear slowly but incompletely.

On the lateral projection of the thorax (Fig. 6*A*) and on the laminagrams (Fig. 7), lobular masses were noted at both lung bases. Because of the shape and posterior location, the possibility of bilateral superior ectopic kidneys was suggested, and on a subsequent intravenous pyelogram, with the patient appropriately positioned, the renal nature of these masses was proved (Fig. 8).

Fig. 5. Normal clearance is noted on the left side. Note the tortuous and elongated left ureter. The density protruding superiorly probably represents the superior pole of the left kidney plus the left adrenal gland.

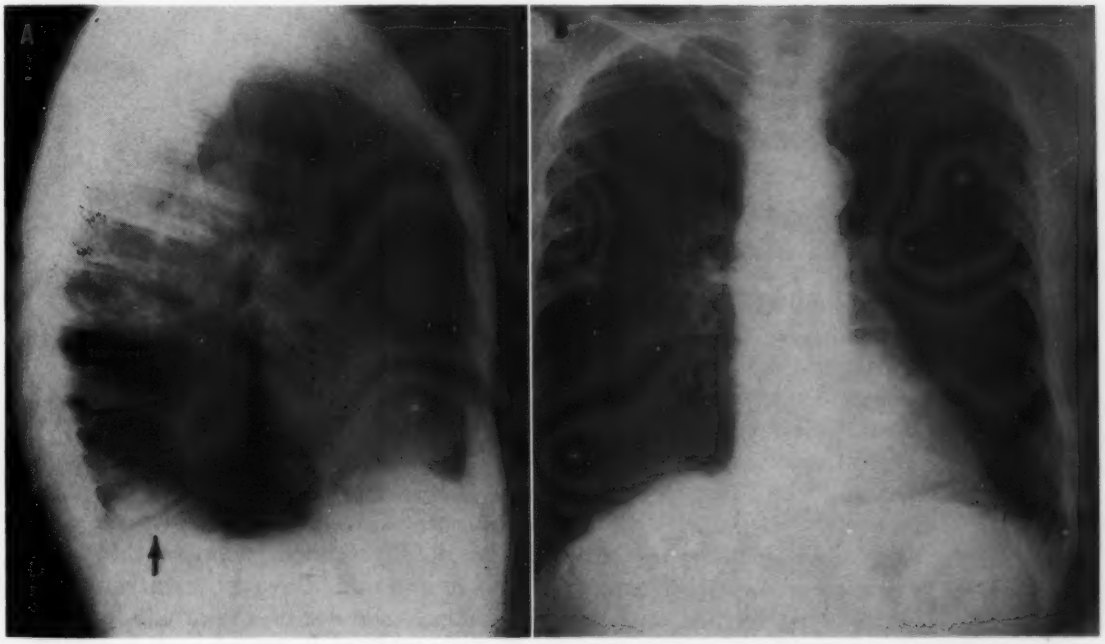


Fig. 6. Roentgenograms of thorax of Case III. The arrow points to the ectopic kidney of the left side, above which projects the superimposed image of the dystopic right kidney. Incidentally, note the abnormal parenchymal changes in the superior aspect of the right lower lobe, and also calcifications outlining aneurysmal changes of the ascending aorta and right sinus of valsalva.[15] (Intracardiac crescenteric calcification seen clearly on original film.)

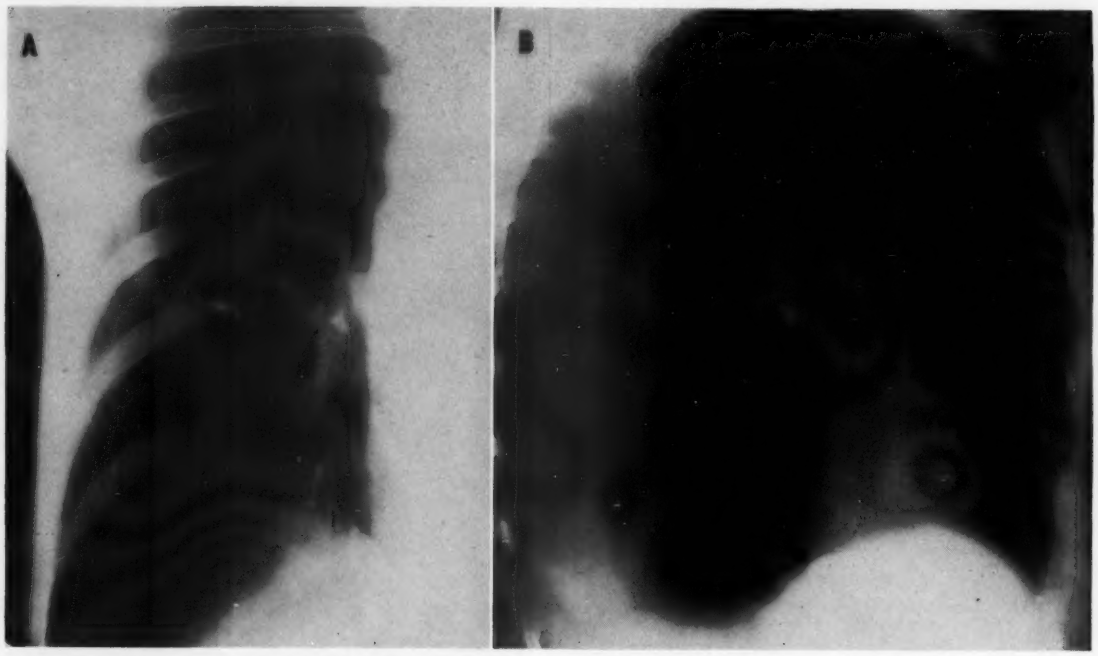


FIG. 7. Laminagrams of the right hemithorax, taken in the anteroposterior position at 5 cm. level (*A*) and in the mid-clavicular sagittal plane (*B*), demonstrate best the reniform mass protruding above the normal diaphragmatic level at the right base, posteriorly.

HISTORIC ASPECTS

In the past, anatomists and pathologists have noted the occurrence of partial or complete thoracic ectopy of the kidney with or without the adrenals in stillborn fetuses and infants, usually associated with gross defects in the diaphragm and accompanied by diaphragmatic herniation of colon, small intestine, and stomach. Gruber,[13] in 1927, collected 11 such cases discovered at autopsy. One year later, Kleine described in the postmortem findings of a stillborn 7 month female fetus a left diaphragmatic defect through which the left adrenal, dome of the left kidney and the intestines had herniated.[14]

Historically, the first documented report of isolated renal ectopy was in 1922 by Mikulicz-Radecki, who described a true congenital diaphragmatic hernia involving the major portion of the right kidney, found in a stillborn 7 month female anencephalic fetus.[16] The herniated kidney exhibited fetal lobulations but appeared normal histologically. It was covered partially by a sac measuring 2.2 cm. in diameter at its neck and situated in the region of the pleuroperitoneal canal (Fig. 9). The sac was formed by a thinned and transparent portion of the right hemidiaphragm devoid of muscle.

INCIDENCE

High dystopy of the kidney is a rarity. Campbell, in 1930, discovered 26 cases of low renal ectopia in 13,000 consecutive autopsies, and only one instance of high ectopy.[8] The patient, a one year old male infant, died of marasmus and at autopsy was found to have an apparent congenital diphragmatic hernia with a large defect in the left diaphragmatic leaflet that admitted 4 fingers and had allowed the entrance into the thorax of most of the left kidney, the major portion of the colon and all of the small intestine, which had compressed the lungs and shifted the mediastinal contents. In a larger collective autopsy series of 207,321 necropsies reported in the literature, Eisendrath and Rolnick, in 1938, dis-

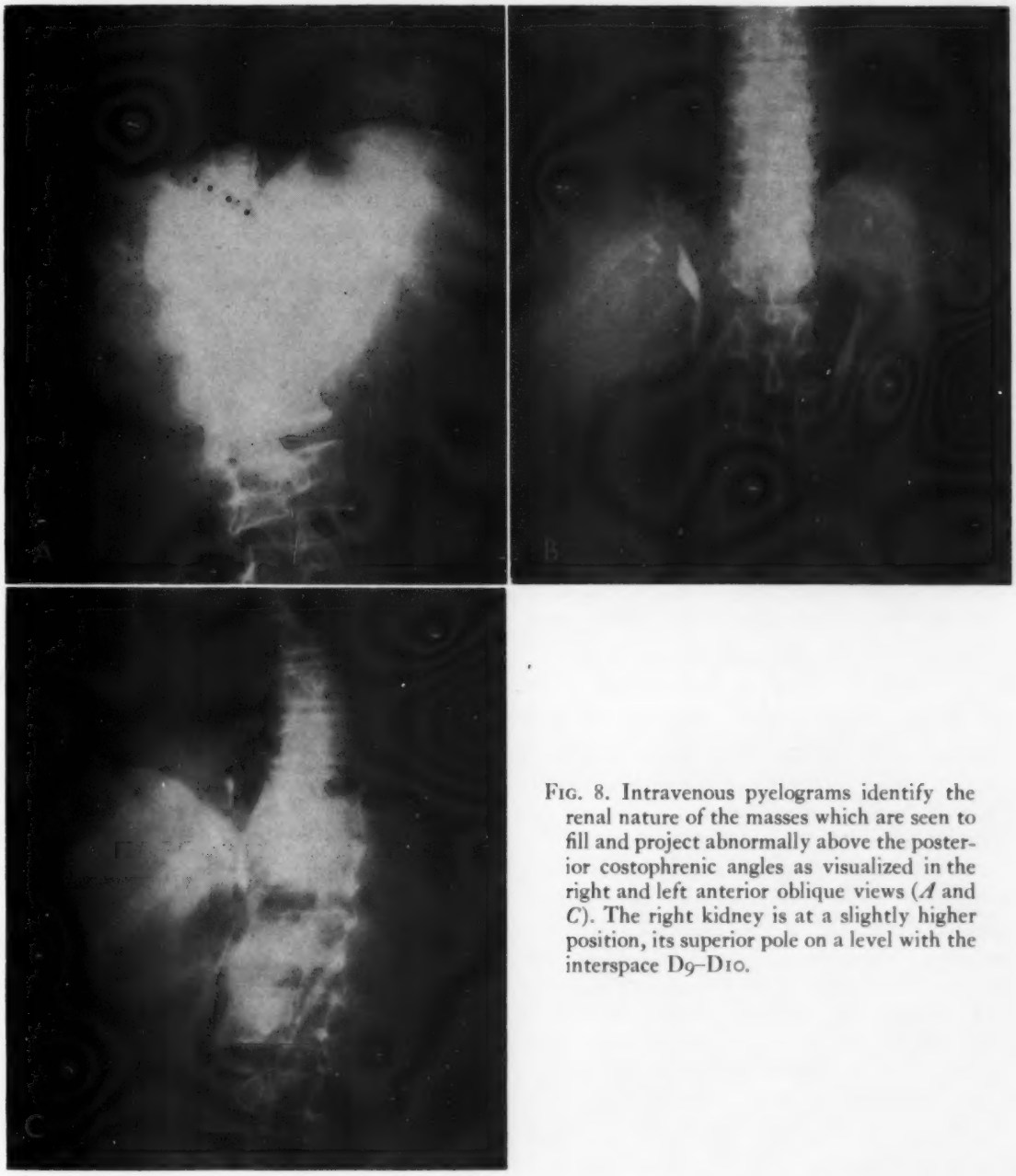


Fig. 8. Intravenous pyelograms identify the renal nature of the masses which are seen to fill and project abnormally above the posterior costophrenic angles as visualized in the right and left anterior oblique views (*A* and *C*). The right kidney is at a slightly higher position, its superior pole on a level with the interspace D9–D10.

covered only 5 cases in which high ectopic kidneys had been found.[10] More recently, in a series of 9,000 chest roentgenograms of newborn infants, Caffey did not observe a single instance of such an anomaly.[7]

In 1939, Baurys and Servoss reported a case of "diaphragmatic eventration" in an adult, which involved a portion of colon, stomach and the left kidney, demonstrated by pyelography.[3] Priority, however, for the diagnosis of the solitary renal anomaly in a living patient must be given to Wolfromm, who in 1940 by means of pyelography identified a "superior dystopy of the right kidney" presumed congenital in nature.[24] The anomaly was discovered in a forty-three year old female during the diagnostic work-up for a mass palpable in the right lower

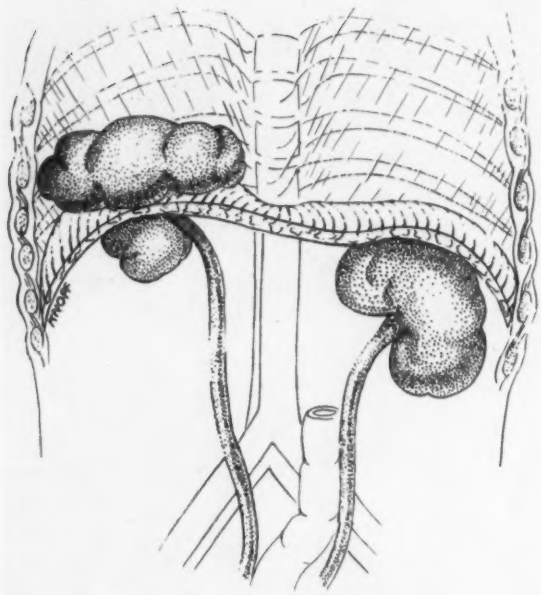


FIG. 9. Sketch adapted from Mikulicz-Radecki of the postmortem finding in the first published case of superior ectopy of the kidney. Note the fetal lobulations and elongated ureter on the right.

quadrant of the abdomen, which at first was considered clinically to be a low ectopic kidney, but which proved roentgenographically to be abdominal viscera displaced inferiorly by the dystopic kidney.

Successful diagnoses of presumed isolated congenital high renal ectopia were subsequently reported by Spillane and Prather,[21] Bugden,[5] Fleischner, Robins and Abrams,[11] Ritvo,[18] Schwartz and Fränkel,[20] Bulgrin and Holmes,[6] Sypniewska,[22] and Gondos.[12]

In this same period, several cases were discovered only after surgery. These were described in texts by Pillmore,[17] Rubin,[19] and in articles by Barrett,[2] Williams and Tillinghast,[23] Bugden,[5] and Bell, Heublein and Hammer.[4] In all but Bugden's report, the patients' histories included severe trauma in the form of stabbings and physical injuries which had caused multiple skeletal fractures. Preoperatively, tumor was suspected in these cases. In 3 instances pneumothorax had been performed, and the unidentified masses were described as extrapulmonary. Postoperatively, traumatic rupture of the diaphragm plus secondary herniation of the kidney was felt to be the basis for the abnormal conditions observed.

In the case reported by Williams and Tillinghast, although the chest roentgenogram was reported as abnormal and an intravenous pyelogram disclosed a normally functioning but elevated left kidney, the findings had not been correlated and a correct preoperative diagnosis was not made. The routine positioning of the patient during pyelography did not include the diaphragmatic leaflets and the abnormal relationship of the left kidney was not appreciated.

The report of Bell *et al.* was of interest in that the suspected "tumor mass" appearing at the right lung base was actually transected surgically and the diaphragmatic defect repaired. The surgical specimen, histologically, contained kidney tissue. An intravenous pyelogram demonstrated a roentgenographically functioning lower renal collecting system observed just below the repaired diaphragm. A second hernia involving this portion occurred six months later and the remainder of the right kidney was then excised.

EMBRYOLOGIC ASPECTS

The complicated process of fusion of the membranous and muscular elements forming the diaphragm is complete by the eighth fetal week. By the same time, normally, the anlage of the adult kidney have joined, established contract with the adrenal and "ascended" to a high lumbar level. The renal and adrenal vascular supply is variable and may include temporary sources.[1,9] These events are apparently unrelated but follow chronologically, so that at birth, ordinarily, the kidney, capped by the adrenal, is retroperitoneal and situated below the posterior aspect of the diaphragm.

The roentgenographic findings and earlier postmortem data disclose several unusual variations. For some unknown cause, the kidney, with or without the adrenal, may ascend abnormally high through an actual gap or bulge and eventrate a portion of the posterolateral aspect of either diaphragmat-

ic leaflet, remaining malrotated in position and associated with an elongated ureter and a high arterial supply. The degree of the renal herniation is variable, and may be an isolated event or associated with practically any one or several of the mobile abdominal viscera.

DISCUSSION

The largest group of cases reported in the literature were those described earlier in collected series of necropsy data of stillborn fetuses or infants. As a rule, there was an associated diaphragmatic herniation of other abdominal viscera suggesting a theoretic evolution. Inasmuch as the kidney is the only subdiaphragmatic organ in a "position" to herniate by virtue of its proximity to the variably thinned gap in the diaphragmatic leaflet at the region of the pleuroperitoneal hiatus, plus its ascent during development, it may be the first to enter the thorax and interfere in part with the normal development of the diaphragm. If the result is a sufficiently large gap or a thinned and weakened membrane, other mobile organs may herniate, especially following the increased intrauterine pressures associated with pregnancy and parturition or the abnormal intra-abdominal pressures in the newborn developed during crying. The isolated renal hernia may then become complicated by the entrance of other organs into the chest, which by their presence might alter cardiopulmonary dynamics and account for the stillbirths and deaths of the infants. The immediate recognition of a diaphragmatic hernia in the newborn infant and, perhaps what is more important, the identification of kidney in an abnormal superior location by pyelography may allow definitive surgery and alter what might otherwise be a fatal progression of events.

It would appear that when isolated and nontraumatic in origin, and restricted sufficiently by the partially eventrated diaphragm, the anomaly remains asymptomatic and is detected only incidentally or accidentally. In such a case, no surgery appears indicated. Its correct identification, however, may be of great aid to the surgeon if the kidney ever becomes diseased and requires definitive treatment. In this regard, high renal ectopy differs from the more common pelvic ectopic kidney which according to Campbell "is as a rule deformed in size and shape, smaller, lobulated and more subject to intrinsic disease." The cases of high renal ectopy diagnosed preoperatively and the cases in which postoperative pyelographic studies were performed demonstrated normal size, shape and urographic function.

Left sided hernia, at any age, according to Bugden should be repaired to prevent other intraperitoneal viscera from herniating especially in the event of subsequent severe trauma to the chest or abdomen. The long, asymptomatic follow-up of Barrett's case, a fifty-two year old male who had been stabbed twenty-six years prior to the discovery of the unidentified mass in the right chest explored as a tumor suspect, would seem to support his view that the presence of the liver offers a protective barrier to the herniation of other organs in cases of right-sided involvement, but a similar history of severe trauma six years preceding the exploratory surgery in Williams and Tillinghast's case (a left-sided herniation) would question the necessity for such prophylactic surgery.

If trauma precedes the finding of a displaced kidney in which renal bleeding may be present and continues or obstructive uropathy results, etc., the same surgical considerations governing the treatment of a normally placed but diseased kidney should be followed.

DIAGNOSIS

Pyelography, with appropriate positioning of the patient, *i.e.*, to include visualization of the diaphragm, will easily establish its renal nature if the case is one of high ectopia of a kidney. If not, fluoroscopy, diagnostic pneumothorax and gastrointestinal series should be performed in the further attempt to identify the mass,

preceding exploratory thoracotomy. The exact localization of the adrenal might have been possible by the use of presacral air insufflation, and the use of pneumoperitoneum combined with pneumothorax would have demonstrated the true status of the diaphragm at the site of the renal ectopy, but these procedures were not deemed necessary or justified in the cases described in this report.

CONCLUSIONS

Although superior ectopia of the kidney apparently represents a rare condition in the literature, the discovery of 3 cases within a relatively short period of time at one institution suggests that its occurrence is greater than suspected. The collected autopsy incidence may not have included cases in which the diaphragmatic leaflet had been merely thinned and partially eventrated, rather than being actually deficient in part. The possibility should, therefore, be considered in the differential diagnosis of a mass situated at the posterior aspect of the base of the lungs. Renal identity may be established with ease by means of pyelography, positioning the patient appropriately to allow visualization and appreciation of the abnormal diaphragm.

SUMMARY

1. Two cases of nontraumatic and presumed congenital superior ectopy of the left kidney (and possibly the adrenal), identified roentgenographically, are described and added to 10 similar cases noted in the literature.

2. An unusual instance of bilaterally high ectopic kidneys, apparently unique in the literature, diagnosed urographically in a third patient is described.

3. The embryologic aspects of the anomaly of superior ectopy of the kidney have been outlined and necropsy data reviewed.

4. A theoretic possibility of life-saving surgery in the newborn found to have superior dystopy of a kidney, which might allow further herniation of other abdominal viscera, is suggested.

5. The implications of noting a reniform mass but not demonstrating its nature are discussed in reference to 6 cases reported earlier that had been unnecessarily operated upon as tumor suspects.

6. The inclusion of the possibility of renal ectopy in the differential diagnosis of lobular masses at the posterior lung base is stressed. Pyelography with a modification of the routine positioning is suggested as an early diagnostic measure. It should precede the gastrointestinal series, pneumothorax, pneumoperitoneum and certainly precede any surgical exploration or excision.

Herbert S. Berlin, M.D.
1041 Bushwick Avenue
Brooklyn 21, New York

We wish to thank Mrs. M. Nesson for her careful transcription of the manuscript, the Department of Medical Illustration for the illustrations and Mrs. K. N. Newerly for her aid in the transalation of the foreign articles.

REFERENCES

1. AREY, L. B. Developmental Anatomy. Sixth edition. W. B. Saunders Company, Philadelphia, 1945, pp. 292–305.
2. BARRETT, N. R. Right retroperitoneal diaphragmatic hernia. *Brit. J. Surg.*, 1945, *32*, 421–425.
3. BAURYS, W., and SERVOSS, S. Eventration of diaphragm; report of case involving kidney. *Urol. & Cutan. Rev.*, 1949, *53*, 535–536.
4. BELL, J. C., HEUBLEIN, G. W., and HAMMER, H. J. Roentgen examination of urinary tract. AM. J. ROENTGENOL. & RAD. THERAPY, 1945, *53*, 527–562.
5. BUGDEN, W. F. Two cases of intra-thoracic kidney. *Dis. of Chest*, 1950, *17*, 357–359.
6. BULGRIN, J. G., and HOLMES, F. H. Eventration of diaphragm with high renal ectopia. *Radiology*, 1955, *64*, 249–251.
7. CAFFEY, J. Personal communication, April, 1956.
8. CAMPBELL, M. F. Renal ectopy. *J. Urol.*, 1930, *24*, 187–198.
9. CAMPBELL, M. F. Urology. Vol. I. W. B. Saunders Company, Philadelphia, 1954, pp. 233–238, 278–279.
10. EISENDRATH, D. N., and ROLNICK, H. C. Urology. Fourth edition. J. B. Lippincott Company, Philadelphia, 1938, p. 599.
11. FLEISCHNER, F. G., ROBINS, S. A., and ABRAMS, M. High renal ectopia and congenital diaphragmatic hernia. *Radiology*, 1950, *55*, 24–26.

12. Gondos, B. High ectopy of left kidney. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1955, *74*, 295–298.
13. Gruber, G. B. In: Schwable-Gruber. Morphology of Malformations of Humans and Animals. Part III. Div. 3, Chap. 2, 1927.
14. Kleine, H. O. Die Bedeutung der intrathorakalen Nierendystopie für die Entstehung kongenitaler Zwerchfellslücken. *Beitr. z. path. Anat. u. z. allg. Path.*, 1928, *80*, 609–621.
15. Merten, C. W., Finby, N., and Steinberg, I. The antemortem diagnosis of syphilitic aneurysm of aortic sinuses. *Am. J. Med.*, 1956, *20*, 345–360.
16. Mikulicz-Radecki, F. Contribution to congenital intra-thoracic dystopy of kidney. *Zentrabl. f. Gynäk.*, 1922, *46*, 1718–1722.
17. Pillmore, G. U. Editor. Clinical Radiology. Vol. I. F. A. Davis Company, Philadelphia, p. 258.
18. Ritvo, M. Chest X-Ray Diagnosis. Lea & Febiger, Philadelphia, 1951, pp. 350–351.
19. Rubin, E. H. Diseases of the Chest. W. B. Saunders Company, Philadelphia, 1948, pp. 533–535.
20. Schwartz, A., and Fränkel, M. High renal ectopia, detected on routine chest examination; case report. *Acta radiol.*, 1952, *37*, 583–585.
21. Spillane, R. J., and Prather, G. C. High renal ectopy; case report. *J. Urol.*, 1949, *62*, 441–445.
22. Sypniewska, M. Superior dystopic kidney. *Polski Przg. Chir.*, 1955, *27*, 467–471.
23. Williams, R. G., and Tillinghast, A. J. Diaphragmatic herniation of kidney. *Radiology*, 1949, *53*, 566–568.
24. Wolfromm, G. Situation du rein dans l'éventration diaphramatique droite. *Mém. Acad. de chir.*, 1940, *66*, 41–47.

HISTOPATHOLOGY OF ROENTGEN DEATH OF YOUNG AXOLOTL (SIREDON MEXICANUM)*

By V. V. BRUNST, Sc.D.
BUFFALO, NEW YORK

FOR an understanding of the biologic effect of roentgen irradiation, comparative radiobiology is important. In our previous papers we compared the effect of the same type of irradiation on different animals—mouse and axolotl.[8,14]

The purpose of this paper is investigation of histopathology of roentgen death after total body and partial irradiation of young axolotl and comparison of these data with histopathology of mammals.

MATERIAL AND METHODS

One hundred and twenty axolotls (Siredon mexicanum) were divided into 7 groups. In the first group, the animals were irradiated totally with 3,000 r 30 days after hatching (Fig. 1). In the second group, the whole body exclusive of the head was irradiated with the same dose 31 days after hatching. In the third group, only the heads of the animals were irradiated with the same dose 31 days after hatching. In the fourth group, the animals were irradiated totally with 6,000 r, 47 days after hatching. In the fifth group, the whole body, exclusive of the head, was irradiated with the same dose 47 days after hatching. In the sixth group, only the head of the animals was irradiated with the same dose, 47 days after hatching. In the last group, 35 animals served as untreated controls.

The irradiations were made under the following conditions: 100 kv., 5 ma., with no external filtration. The target-object distance was 18 cm. Under such conditions, the intensity was 206 r/min. During irradiation, the animals were anesthetized by means of a weak aqueous solution of tricaine methane-sulfonate (M.S. 222). They were placed on a piece of cardboard covered with wax paper and several layers of moistened filter paper. For total body irradiation the area 6–7 cm. in diameter was surrounded by moistened cotton. The animals were placed in this "container" during treatment. For irradiation of the head only or for irradiation of the whole body exclusive of the head, the nonirradiated portions were shielded with a lead covering (made from a 4 mm. lead sheet) with a round radiation localizer 6.5 cm. in diameter.[6] The animals were situated in radial position during the treatment. Immediately after irradiation, the animals were put into water, where they recovered from the anesthesia. During the first months after irradiation, 1 animal was sacrificed and fixed every week. If the animals of some particular experiment survived for a long period of time, the fixations were made once a month or less often. Some animals were fixed eight months after irradiation. Fixations were made in saturated solution of bichloride of mercury with 5 per cent acetic acid. The material was embedded in paraffin with 5 per cent beeswax. The sections were cut at 8 μ and stained with Ehrlich's hematoxylin and eosin. The photomicrographs were made of parts of sections under lowest (×35), low (×100), high (×450 and ×500), and highest (×900) magnifications.

RESULTS

For convenience of consideration of the histopathology of death, we distributed the material according to the different tissues and organs, which were investigated.

1. *The Epithelium of the Skin and Subcutaneous Pigment Layer*

a. Changes in the skin epithelium are very important for evaluation of irradiation effects. Such changes were described

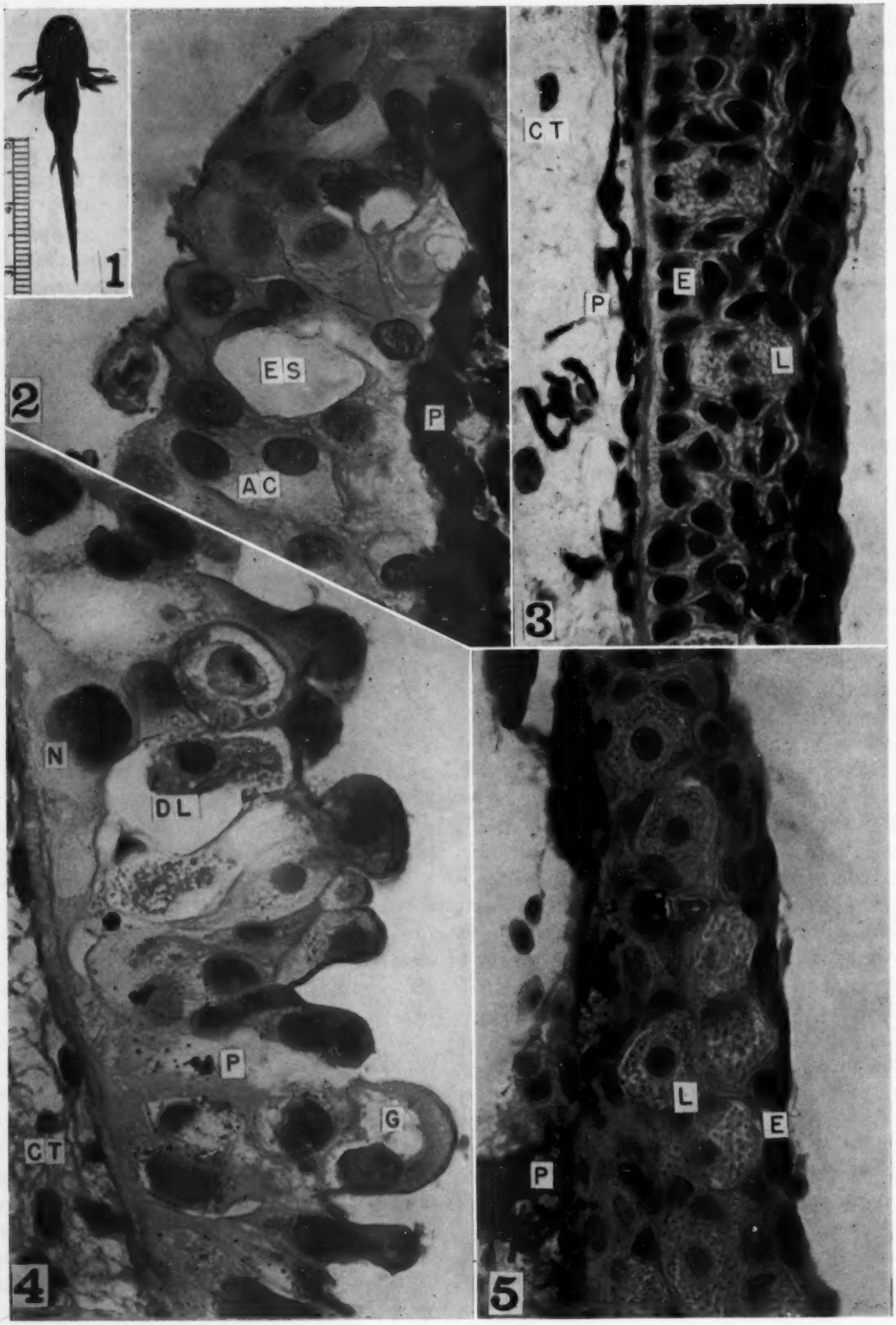
* Laboratory of Radiobiology, Roswell Park Memorial Institute.
This work was supported by grant No. C-2549 of the United States Public Health Service.

after local roentgen irradiation in our previous papers.[11] Usually formation of abnormally large and giant cells was observed. In the present material, after total body irradiation and after irradiation of whole body, exclusive of the head, a similar picture could be seen. It is noteworthy that the formation of giant epithelial cells occurred also after irradiation of mammals.[14,17] The photomicrograph in Figure 2 shows the picture of moderate damage of the epithelium 39 days after roentgen irradiation with 3,000 r. Comparison with normal epithelium of control animal (Fig. 3) shows that all cells of irradiated epithelium in this region are abnormally large. The photomicrograph in Figure 4 shows the serious damage of skin epithelium 25 days after treatment with 6,000 r. The gradual disappearance of Leidiger cells and formation of typical "giant cell degenerating epithelium" can be noted. Such cells were described after local irradiation during the primary acute reaction.[4,11] In this epithelium the nuclei of epithelial cells in some places are very large. The presence of chromatine granules and a nucleolus is typical. The accumulation of small pigment particles in some cells can be observed (Fig. 4). The damage of epithelium after irradiation was noted in 73 per cent of all cases. It was seen in 85 per cent of all animals fixed during the primary acute reaction (between 20 and 60 days after irradiation). After the end of this reaction (60 days or later) the epithelium was normal in appearance in 100 per cent of the cases. For example: the photomicrographs of the skin epithelium of an animal fixed 102 days after irradiation with 3,000 r show that size and appearance of the epithelial cells are not distinguishable from the epithelium of control animals (Fig. 5). The difference in number of Leidiger cells which can be noted (compare Fig. 3 and 5) is represented very often in various regions of skin epithelium of normal animals. This is not connected in any case with the effect of roentgen irradiation. The uneven outside surface of degenerating giant cell epithelium (Fig. 4) disappeared and was replaced with the even surface of normal-looking epithelium (Fig. 5).

b. The subcutaneous pigment layer in most cases is completely normal in appearance. Only in 19 per cent of all cases, slight damage of this layer was noted, but if the great variety in number of pigment cells in normal axolotl is taken into consideration, it is very difficult to distinguish slight damage of the pigment layer from the normal condition. Therefore, it is very possible that real damage of the pigment layer occurs in much less than 19 per cent of the animals. In any case, it is clear that degenerating globular pigment cells are exceptionally rare in this material. This is a very unexpected result because after local irradiation of certain regions of the axolotl body, a reduction of the pigment layer almost always occurred.[12] In our previous studies, only isolated normal pigment was observed after local irradiation, while almost all pigment cells are normal in the present material.

2. *The Loose Connective Tissue*

Changes in loose connective tissue after local irradiation were not described in our previous paper. But in the present material after total body irradiation and after irradiation of whole body exclusive of the head, partial damage of loose connective tissue was observed very often (in 85 per cent of the cases). In most cases, formation of giant cells in irradiated connective tissue was seen. For example, such giant cells appeared in the tissue of dead or dying animals 26–27 days after total body irradiation with 6,000 r (Fig. 6 and 8). But it was easy to find loose connective tissue absolutely normal in appearance (Fig. 7), which was not distinguishable from the same tissue of control animals (Fig. 9), in other regions of animals irradiated with the same dose and fixed at the same time (the difference in fibers can be observed in various portions of normal animals). The difference in size between giant loose connective tissue cells and normal cells of the same


1
2
ES
P
AC
3
CT
E
P
L
4
N
DL
P
G
CT
5
L
E
P

kind is very great (compare Fig. 6 and 8 with 7 and 9). Probably these cells are abnormally large fibroblasts. They have in most cases very large oval nuclei with a large number of coarse chromatin granules, which are clearly seen because they are stained darkly by hematoxylin (Fig. 6, G). These cells are clearly distinguishable from macrophages, which were always observed after local irradiation of tail or limb of axolotl.[12] It is possible to find occasional macrophages in the present material in the group in which the whole body, exclusive of the head, was irradiated (Fig. 10 and 11). The main difference between these two types of cells is the following: the normal and giant fibroblasts have a very clear protoplasm which is almost impossible to see by the staining technique employed (Fig. 6, 7 and 9). The macrophages, according to our observations, have very dark stained granular protoplasm (Fig. 10 and 11). In the giant fibroblast the formation of real pseudopodia is not observed and they do not have phagocytic ability. For the macrophages, on the contrary, formation of pseudopodia is typical and they have phagocytic ability and therefore often play a very active role in destruction of damaged tissues after roentgen irradiation. For example, the reduction of cartilaginous skeleton in irradiated limb is the result of activity of macrophages.[5] After local irradiation, the macrophages often were observed in great number in the region of reduction. Such great accumulation of macrophages was not observed in the present material. Only isolated macrophages were found during reduction of limbs or tails of animals with irradiated whole body, exclusive of the head. Possibly they originated from the nonirradiated tissues of the head, but we have no evidence of this. The phagocytic activity of macrophages was apparent in the present material also (Fig. 11, FM). The presence of various types of inclusions, which are very typical for macrophages, is obviously the result of phagocytosis. Such inclusions were not seen in the giant fibroblasts. The giant fibroblasts accumulated in some regions of irradiated animals in such numbers that the appearance of connective tissue contrasted very much with the normal connective tissue of control animals.

Various gradations of abnormally large cells or giant cells were noted in various types of connective tissues. For example, giant cells were observed in loose connective tissue (see above), while abnormally large cells were seen in connective tissue between cartilaginous skeletal elements (interskeletal connective tissue, Fig. 12 and 13) or in very dense connective tissue surrounding the cloaca (Fig. 14 and 15).

The mitotic activity in irradiated loose connective tissue was usually suppressed (Fig. 14), but in some cases it was possible to find isolated mitotic figures, which were usually abnormal. Abnormal distribution of chromosomes (Fig. 16) and multipolar mitotic figures (Fig. 17) were observed.

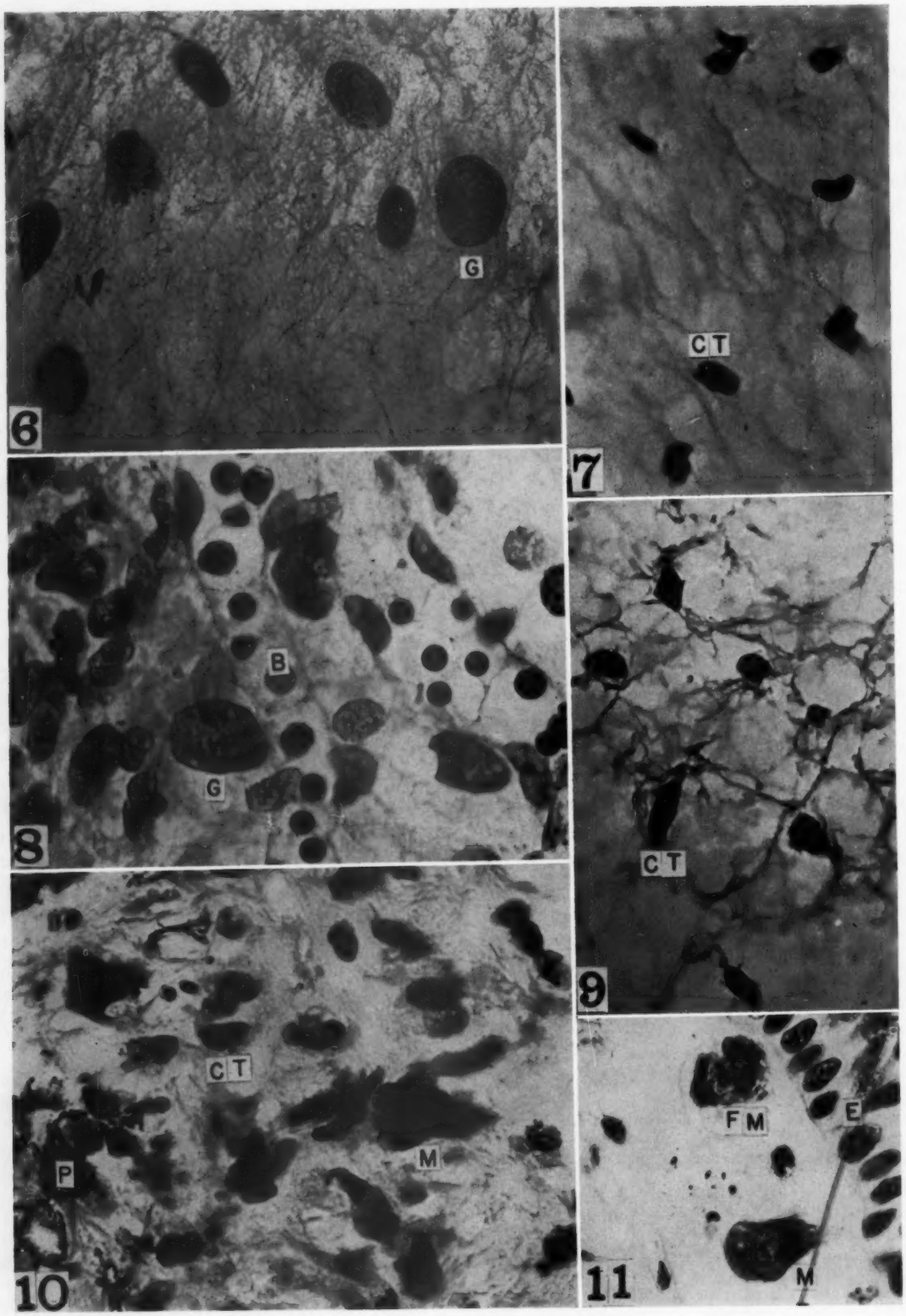
Fig. 1–5. 1. The axolotl 31 days after hatching on day of irradiation.

2. Part of the section through the tail of axolotl (No. 48) 39 days after irradiation with 3,000 r of whole body exclusive of the head and 70 days after hatching. Abnormal skin epithelium. (AC) Abnormally large epithelial cells; (E.S.) empty space from degenerated Leidiger cell; (P) pigment layer. Photomicrograph ×450.

3. Part of the section through the tail of control animal 169 days after hatching. (E) Epithelial cells; (L) Leidiger cell; (P) pigment layer; (CT) connective tissue cell. Photomicrograph ×450.

4. Part of the section through the hind limb of axolotl (No. 93), 25 days after irradiation with 6,000 r of whole body exclusive of the head and 72 days after hatching. Typical giant cell degenerating epithelium. (CT) Connective tissue cells; (DL) degenerating Leidiger cell; (G) giant epithelial cell; (N) especially large nucleus of giant epithelial cell; (P) pigment. Photomicrograph, ×450.

5. Part of the section through the body of axolotl (No. 54) 102 days after irradiation of whole body exclusive of the head with 3,000 r and 133 days after hatching. Skin epithelium is normal in appearance. (E) Epithelial cells; (L) Leidiger cell; (P) pigment cells. Photomicrograph, ×450.


G
6
CT
7
B
G
8
CT
9
CT
P
M
10
FM
E
M
11

The peculiar type of giant cells is shown in Figures 18 and 19. They are quite similar to the prochondrial cells of normal axolotl, but prochondrial cells are situated in close proximity to cartilaginous skeletal elements (Fig. 25), while these abnormal cells are distributed in loose connective tissue and in some cases form dense accumulation (Fig. 19).

3. *The Cartilage*

Definite damage in cartilaginous tissue occurred comparatively infrequently (in 25 per cent of all cases). Even in the longest surviving animals, which died 28 days after total body irradiation with 6,000 r, the appearance of cartilaginous skeleton in limbs was normal. It is noteworthy that differentiation of skeletal elements of the tarsus was completely correct (Fig. 23), and that in spite of irradiation with lethal dose, the morphogenesis was not disturbed. Obviously the animals died too soon and reaction of cartilaginous tissue is too slow to show any obvious irradiation damage in most cases. According to Domagk,[16] the damage in cartilage of mammals can be observed only after irradiation with very large doses.

In some cases it was possible to see damage of cartilaginous tissue. In another animal of the same experimental group (total body irradiation with 6,000 r), sacrificed and fixed also 28 days after treatment (the last surviving animal in this group), the cartilaginous skeleton at the limb was abnormal (Fig. 24 and 26). The comparison with cartilaginous skeleton of a control animal (Fig. 25) showed that most of the cells in irradiated cartilage are very large or even giant, and that many abnormalities in nuclei were present. Some cells were multinucleated (Fig. 24, MC). In many cells fragmentation of nucleus was observed. Due to this process, formation of different sizes and numbers of various forms of nuclear fragments resulted (Fig. 24, AC and 26, AC). In another animal (Fig. 27) irradiated with the same dose (6,000 r) and approximately at the same time after treatment, much smaller abnormalities were observed. Some nuclei were larger than normal (Fig. 27, LN), but cells were normal in size. The nuclear abnormalities were seen only in rare cases.

4. *The Muscles*

Damage of muscles was noted in only 15 per cent of all cases. In most cases the appearance of muscles even after irradiation with 6,000 r was normal (Fig. 22). Only in comparatively rare cases were abnormalities noted in the structure of muscle nuclei.

Figure 20 shows the maximum damage to muscle that was found. The comparison with normal muscles of control animals (Fig. 21) shows that in irradiated muscles

---

Fig. 6–11. 6. Part of the section through the body of axolotl (No. 64) 27 days after total body irradiation with 6,000 r and 72 days after hatching. Abnormal loose connective tissue. (G) Giant fibroblast. Photomicrograph ×450.

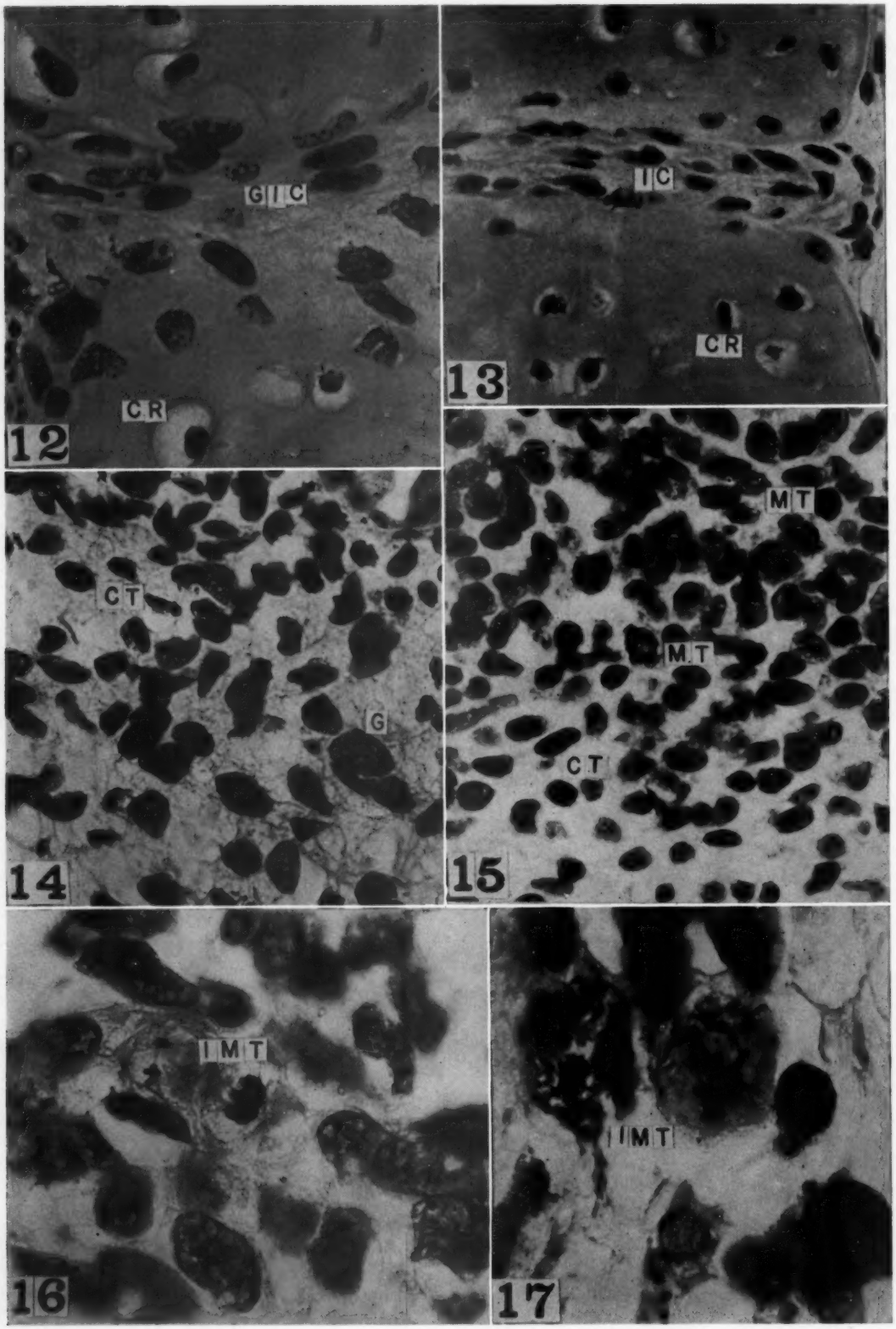
7. Part of the section through the body of axolotl (No. 67) which died 28 days after total body irradiation with 6,000 r and 74 days after hatching. The loose connective tissue is of normal appearance. (CT) Connective tissue cell (fibroblast). Photomicrograph, ×450.

8. Part of the section through the body of dying axolotl (No. 77) 26 days after irradiation of whole body exclusive of the head with 6,000 r and 73 days after hatching. Abnormal loose connective tissue. (B) Blood vessel; (G) giant connective tissue cell (fibroblast). Photomicrograph, ×450.

9. Part of the section through the body of control animal 67 days after hatching. (CT) Connective tissue cell (fibroblast). Photomicrograph, ×450.

10. Part of the section through the body of axolotl (No. 76) 26 days after irradiation of whole body exclusive of the head with 6,000 r and 73 days after hatching. Macrophages in loose connective tissue. (CT) Connective tissue cell; (M) macrophage; (P) pigment cell. Photomicrograph, ×450.

11. Part of the section through the hind limb of axolotl (No. 51) after irradiation of whole body exclusive of the head with 3,000 r and 81 days after hatching. (E) Epithelium; (FM) phagocytosis of macrophage; (M) macrophage. Photomicrograph, ×450.


GIC
CR
12
IC
CR
13
CT
G
14
MT
MT
CT
15
IMT
16
IMT
17

the nuclei are a little larger than usual and sometimes have abnormal shape, but if the great variety in size and shape of nuclei observed in normal muscles is taken into consideration, we come to the conclusion that this damage is very slight and not too definite. The damage of muscle fibers, which was described after local irradiation with 7,500 r of tails of tadpoles of Pelobates fuscus[29] was not observed in present material. According to Rugh,[26] the muscles are the most resistant tissue in the larva of Amblystoma opacum. There was no evidence of injury of the myoplasm or myofibrillae of the muscle. According to Domagk,[16] the muscles in mammals are comparatively radioresistant.

5. *The Spleen*

The reaction of the spleen is important for evaluation of irradiation effect. The damage of the spleen was observed in 56 per cent of all cases.

In dying axolotls after irradiation with 6,000 r, the spleen can be much larger than normal (Fig. 28 and 29) and have signs of damage in some places. According to Rugh, Levy and Sapadin,[27] after total body irradiation of the hamster with 1,500 r, enlargement of the spleen was observed in some cases.

The number of lymphocytes was greatly reduced in certain regions of irradiated spleen, but in spite of this, normal mitotic figures have been noted in some places of the same organ (Fig. 33). In the other cases, the damage of the spleen was more uniform in all regions. Such a picture was possible to see in the longest surviving animal after total body irradiation with 3,000 r (Fig. 30). The abnormality of this spleen was clear by comparison with normal spleen of control animal (Fig. 32). In the irradiated spleen, the number of cells was greatly reduced and the presence of a limited number of unusually large cells with granulated protoplasm was typical (Fig. 30 and 31, SC). These cells were not present in normal spleens.

It was possible to find in some animals (after total body or partial irradiation) with obvious damage of other tissues, for example skin epithelium, the spleen completely normal in appearance.

6. *The Lymph Nodes*

In normal axolotls several pairs of large lymph nodes are situated in the dorso-postero-lateral region of the head (boundary region between head and trunk). They are so large and usually stain so densely that it is very easy to find them on the slide even without a microscope. They are always located on the same plane as the eyes; therefore, in sagittal and frontal sections, it is possible to find them on the same sections that have eyes.

After total body irradiation with 3,000 r

Fig. 12–17. 12. Part of the section through the limb of axolotl (No. 67) 28 days after total body irradiation with 6,000 r and 75 days after hatching. (CR) Abnormally large cartilaginous cell; (GIC) giant intercartilaginous connective tissue cells. Photomicrograph, ×450.

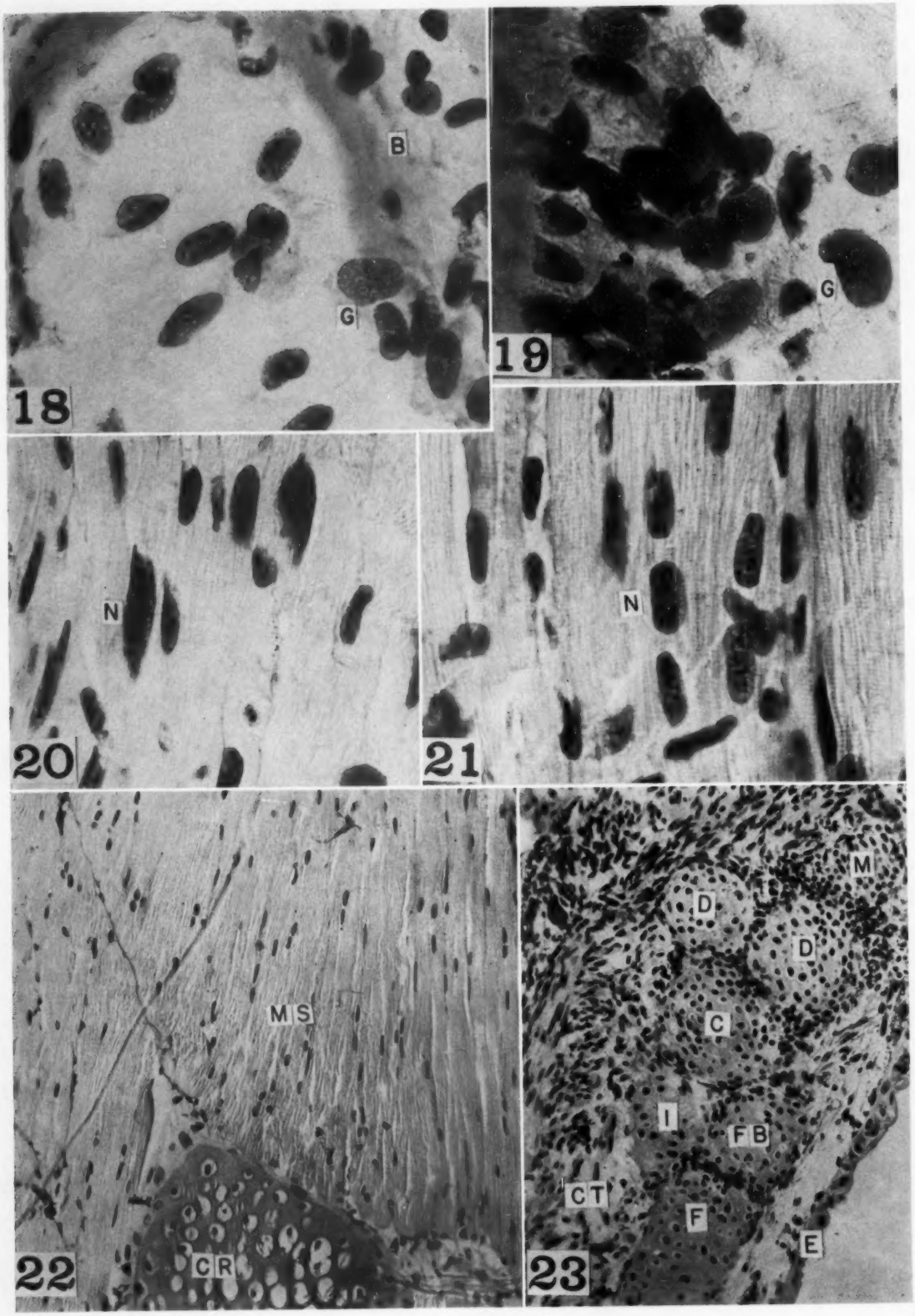
13. Part of the section through the limb of control animal (No. 32) 75 days after hatching. (CR) Cartilaginous cell; (IC) intercartilaginous connective tissue cells. Photomicrograph, ×450.

14. Part of the section through the body of axolotl (No. 68) 28 days after total body irradiation with 6,000 r and 75 days after hatching. Connective tissue surrounding the cloaca. (CT) Connective tissue cells of normal size; (G) giant connective tissue cell. Photomicrograph, ×450.

15. Part of the section through the body of control animal 38 days after hatching. Connective tissue surrounding the cloaca. (CT) Connective tissue cells; (MT) mitotic figure. Photomicrograph, ×450.

16. Part of the section through the body of axolotl (No. 51) 49 days after irradiation of whole body exclusive of the head with 3,000 r and 81 days after hatching. Connective tissue surrounding the cloaca. (IMT) Irregular mitotic figure. Photomicrograph, ×900.

17. Part of the section through the hind limb of axolotl (No. 51) 49 days after irradiation of whole body exclusive of the head with 3,000 r and 81 days after hatching. Loose connective tissue in limb. (IMT) Two irregular mitotic figures. Photomicrograph, ×900.


B
G
18
G
19
N
20
N
21
MS
CR
22
M
D
D
C
I
FB
CT
F
E
23

and 6,000 r, these lymph nodes were seriously damaged in all cases. In 75 per cent of all cases, they disappeared completely and in 25 per cent, only a small remnant of abnormal lymph nodes could be found. In the latter cases, these lymph nodes consisted of small accumulations of abnormally large lymphoid cells. Abnormally large vessels were observed inside of these lymph nodes. The mitotic activity, which is very typical of normal lymph nodes, was completely suppressed.

7. *The Liver*

Damage of the liver resulted in 64 per cent of the cases, but only in 8 per cent of them could this damage be evaluated as serious. In a great majority of cases, the damage was very slight. In such a case only one abnormality was observed—some of the liver nuclei were enlarged. According to Domagk,[16] damage of the liver of mammals after irradiation can be observed comparatively often.

The liver of an animal that died 28 days after total body irradiation with 6,000 r can serve as an example of severe damage of this organ (Fig. 34). It is clear, in this case, that the number of liver cells is greatly reduced and the sinusoid spaces are greatly enlarged. The mitotic activity is usually suppressed. The appearance of normal liver of control animals is quite different (Fig. 35). The cells and nuclei of normal liver are much smaller. The protoplasm of normal liver cells is dense and granular, and the sinusoids are much smaller. The presence of mitotic figures in the peripheral region is especially typical of normal liver (Fig. 35—see below). Another type of liver damage occurred in an animal which died 25 days after total body irradiation with 6,000 r (Fig. 36). In this case the number of liver cells and size of sinusoids were normal, but the nuclei of the liver cells were definitely larger than normal. This damage can be considered as slight. A similar picture was observed in most cases of irradiation damage of the liver. In an animal which died 102 days after irradiation of whole body exclusive of the head with 3,000 r (Fig. 37), the size of the liver cell nuclei was normal, but the sinusoids were larger than usual. The formation of giant cells with very large nuclei such as in epithelium of the skin was not seen.

It is noteworthy that changes occurred in the liver of animals when only the head was irradiated. Probably changes in metabolism provoke abnormal accumulation of pigment cells in the liver. In some animals these pigment cells accumulated in such number that all of the liver had a black color and only in some places was it possible to see the usual liver cells. For example, such an accumulation of pigment cells may be seen in the liver of an animal fixed 45 days after irradiation of the head only with

Fig. 18–23. 18. Part of the section through the body of axolotl (No. 51) 49 days after irradiation of whole body exclusive of the head with 3,000 r and 81 days after hatching. Giant cells near the bone. (B) Bone; (G) giant cells. Photomicrograph, ×450.

19. Part of the section through the body of axolotl (No. 63) 25 days after total body irradiation with 6,000 r and 72 days after hatching. Giant cells (G) in loose connective tissue. Photomicrograph, ×500.

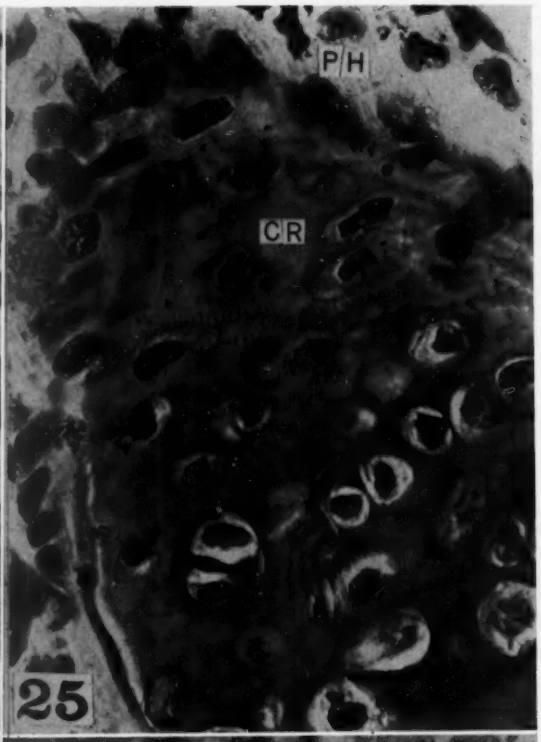
20. Part of the section through the limb of axolotl (No. 68) 28 days after total body irradiation with 6,000 r and 75 days after hatching. The last surviving animal in experiment. Muscles. (N) Nucleus. Photomicrograph, ×450.

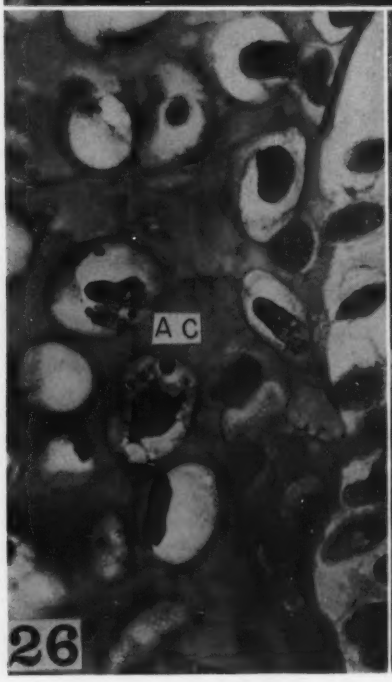
21. Part of the section through the limb of control animal 34 days after hatching. Muscles. (N) Nucleus. Photomicrograph, ×450.

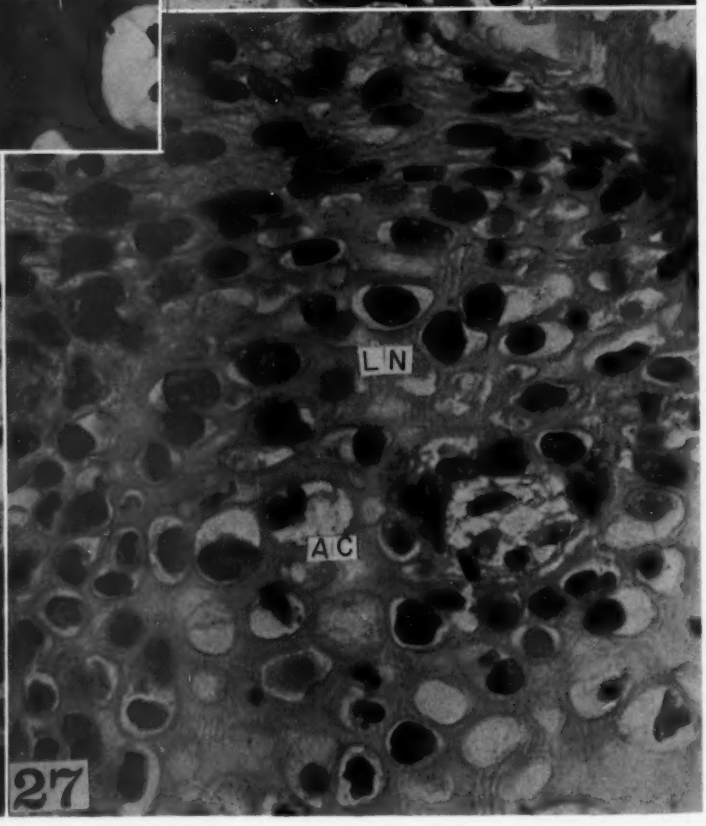
22. Part of the section through the body of axolotl (No. 66) 26 days after total body irradiation with 6,000 r and 73 days after hatching. (CR) Cartilage; (MS) muscles. Photomicrograph, ×100.

23. Part of the section through the hind limb of axolotl (No. 67) which died 28 days after total body irradiation with 6,000 r and 75 days after hatching. Normal appearance of tissues. (C) Centrale; (D) tarsalia distalia; (CT) loose connective tissue; (E) skin epithelium; (F) fibula; (FB) fibulare; (M) metatarsale. Photomicrograph, ×100.

AC
LC
MC
24


PH
CR
25


AC
26


LN
AC
27

3,000 r (Fig. 40). A great variety in the number of pigment cells was observed in animals with head irradiated. The liver of an animal fixed 92 days after irradiation of the head with 3,000 r is an example of one of the smallest number of pigment cells in this organ (Fig. 41), but this number of pigment cells is still much greater than the largest number which is observed in the liver of the control animal of the same age (Fig. 42). Normal animals of this age often have almost no pigment cells in the liver. In any case, the increase in the number of pigment cells in animals with head irradiated is obvious.

8. *The Peripheral Portion of the Liver*

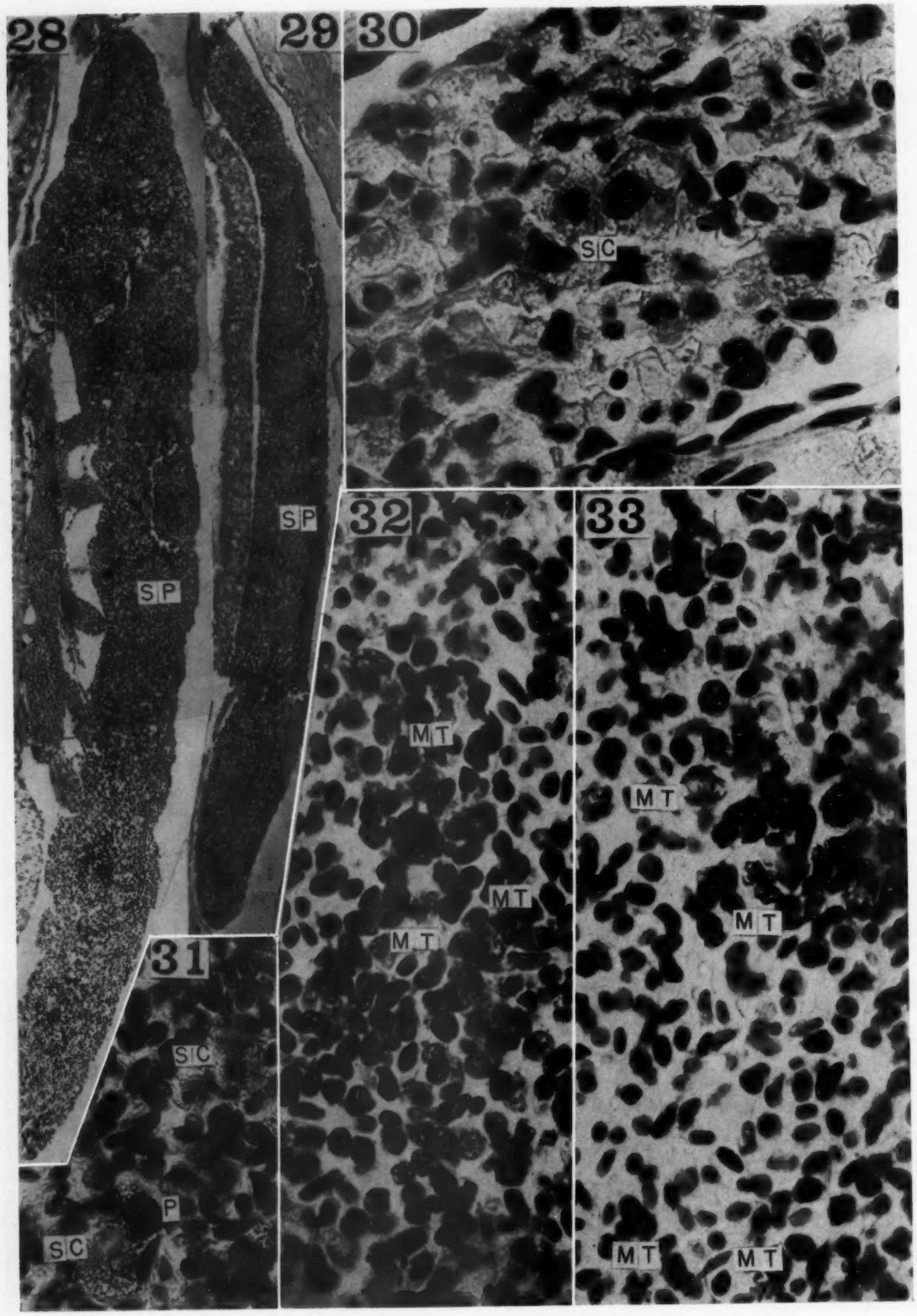
It is necessary to consider the peripheral portion of the liver separately because this portion of the liver of axolotls has a structure and function completely different from all the other portions of the liver (Fig. 38). This is typical lymphoid tissue, which is very similar to lymph nodes and spleen. Many mitotic figures are present in this region of the liver (Fig. 35). Like other lymphoid organs, this portion of the liver is very sensitive to roentgen irradiation. After total body irradiation with 3,000 r or 6,000 r this tissue completely disappeared in 100 per cent of the animals (Fig. 39). However, a different picture resulted from partial irradiation. Therefore, it is important to consider the result of irradiation in each group of experiments separately. In 50 per cent of the animals where the whole body exclusive of the head was irradiated with 6,000 r, the lymphoid tissue completely disappeared, and in 33 per cent, more or less great reduction of the number of lymphoid cells was observed. In 17 per cent, the appearance of this tissue in the liver was normal. Figure 55 shows an example of peripheral lymphoid tissue of the liver with a reduced number of cells. In 71 per cent of the cases where the whole body exclusive of the head was irradiated with 3,000 r, the lymphoid tissue was normal in appearance. All other animals of this group had more or less great reduction of the number of lymphoid cells. It is clear now that the effect of irradiation upon peripheral portions of the liver was quite different in various experimental groups. It is clear also that protection of the head alters in some way the irradiation effect upon the peripheral portion of the liver. One possible mechanism can be suggested to explain this observation. It was mentioned earlier that several pairs of large lymph nodes are located in the dorso-postero-lateral portion of the head. It is very possible that these lymph nodes were shielded only in a part of the head-protected group since their significance was not known at the start of the experiment. In other cases the lymph nodes may have been partially shielded. Where intact lymph node tissue remained, the immature lymphatic cells probably could be transferred by the blood stream to the liver, to promote the recovery of lymphatic tissue in the peripheral portion of the liver. After irradiation with 3,000 r the recovery of this portion of the liver really was observed. Early fixations showed more or less damaged lymphatic tissue of the liver, but in all animals fixed later, this portion of the liver was normal in appear-

Fig. 24–27. 24. Part of the section through the limb of axolotl (No. 68) 28 days after total body irradiation with 6,000 r and 75 days after hatching. The last surviving animal in experiment. Cartilage. (AC) Abnormal cartilaginous cell; (LC) large cartilaginous cell; (MC) multinuclear cell. Photomicrograph, ×450.

25. Part of the section through the limb of control animal 38 days after hatching. (CR) Cartilaginous cells; (PH) prochondral cells. Photomicrograph, ×450.

26. Part of the section through the limb of the animal (No. 68; see Fig. 24). (AC) Abnormal cartilaginous cell. Photomicrograph, ×450.

27. Part of the section through the limb of dying axolotl (No. 77, the last surviving animal in experiment) 26 days after irradiation of whole body exclusive of the head with 6,000 r and 73 days after hatching. (AC) Abnormal cartilaginous cell; (LN) cells with abnormally large nucleus.


28
29
30
SC
SP
SP
32
33
MT
MT
MT
MT
MT
MT
MT
31
SC
P
SC

ance. We have no evidence of the correctness of this hypothesis, but it would explain the fact that in 100 per cent of cases after total body irradiation with 3,000 r, the lymphatic peripheral portion of the liver disappeared completely, while after irradiation with the same dose to the whole body, exclusive of the head, this portion of the liver was normal in appearance in 71 per cent of all cases.

9. *The Kidney*

Damage of the kidney was observed in 35 per cent of the cases. In 15 per cent the damage can be considered as severe. It is noteworthy that damage to the kidney can be found in animals during the primary acute reaction and also in some instances in animals which survive for comparatively long periods of time after the ending of the primary acute reaction. This damage was observed especially in the group of experimental animals, when the whole body exclusive of the head was irradiated with 3,000 r. In some surviving animals of this group edema of whole body with a great accumulation of fluid was an obvious result of kidney damage. Investigation of animals with edema confirms this conclusion. In these animals great damage of kidney epithelium was determined. Many cells of this epithelium were very large, with giant nuclei (Fig. 43). Various sizes of coarse chromatin granules were observed in these nuclei. The mitotic activity in the kidney epithelium of irradiated animals obviously was suppressed. In control animals, the normal kidney epithelium consists of comparatively small cells in which mitotic figures can be observed in some places (Fig. 44). According to Domagk,[16] limited sensitivity to irradiation was observed in the kidney of mammals.

10. *The Intestinal Tract*

The intestinal tract is one of the most sensitive portions of the axolotl body to roentgen irradiation. The injury of the small intestine appeared in 75 per cent of all cases, but in a great majority of cases this damage was slight and very similar to that in the liver, consisting of enlargement of nuclei of the intestinal epithelium (Fig. 48 and 49). In only 11 per cent of the cases this damage was more serious, and formation of giant cells in intestinal epithelium occurred. Even in such cases the damage was much less than in the cloacal region, which, according to our observations, is the most sensitive portion of the intestinal tract to roentgen irradiation. Damage of the cloacal region was observed in 94 per cent of all cases and was very serious in 35 per cent of the cases. The cloacal region of normal axolotls has a very specific pattern. Many deep folds of cloacal epithelium and great accumulation of loose connective tissue with very great number of cells (Fig.

Fig. 28–33. 28. Part of the section through the body of dying axolotl (No. 77) 26 days after irradiation of whole body exclusive of the head with 6,000 r and 73 days after hatching. (SP) Spleen. Photomicrograph, ×35.

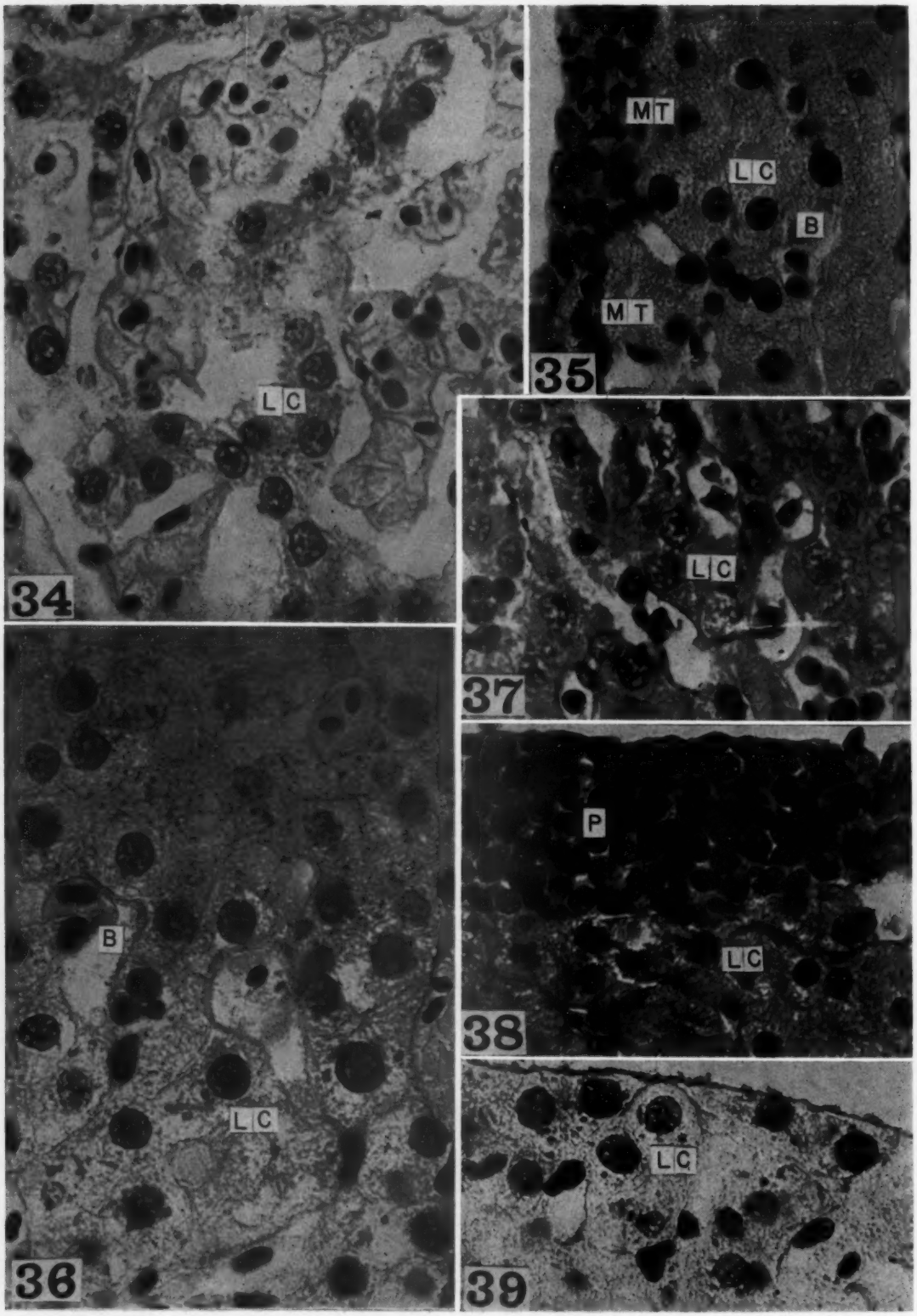
29. Part of the section through the body of control animal 66 days after hatching. (SP) Spleen. Photomicrograph, ×35.

30. Part of the section through the spleen of axolotl (No. 14, the last surviving animal in this experiment) 38 days after total body irradiation with 3,000 r and 69 days after hatching. (SC) Special type of cells. Photomicrograph, ×450.

31. Part of the section through the spleen of axolotl (No. 94, the last surviving animal in this experiment) 183 days after irradiation of whole body exclusive of the head with 6,000 r and 232 days after hatching. (SC) Special type of cells; (P) pigment. Photomicrograph, ×450.

32. Part of the section through the spleen of control animal 68 days after hatching. (MT) Mitotic figure. Photomicrograph, ×450.

33. Part of the section through the spleen of dying axolotl (No. 77, the last surviving animal in experiment) 26 days after irradiation of whole body exclusive of the head with 6,000 r and 73 days after hatching. (MT) Mitotic figure. Photomicrograph, ×450.


LC
34
MT
LC
B
MT
35
LC
37
B
LC
36
P
LC
38
LC
39

46) are typical of this region. The epithelium of the cloacal region of normal animals is typical stratified columnar epithelium (Fig. 46). All of this changed greatly after irradiation and it may be impossible to find another region of the axolotl body in which the general pattern and all components suffer such great changes as in the cloacal region. The typical folds of the cloacal wall completely disappeared (Fig. 45) and stratified columnar epithelium was transformed into abnormal simple columnar. A very great difference in the size of cells of this epithelium is typical. Between the slightly enlarged cells, it was possible to see giant cells with very large nuclei (Fig. 47). In these giant nuclei, large and irregular chromatin granules were observed. Degeneration of this epithelium is clear. It is noteworthy that all animals with great changes in cloacal region died or were sacrificed and fixed during the primary acute reaction. The typical changes in this region during this reaction can be compared only with such changes in the skin epithelium. The number of connective tissue cells surrounding the cloaca was greatly reduced in irradiated animals (Fig. 45) and between the usual connective tissue cells, it was possible to find many abnormally large cells and giant cells. A typical picture of a reaction of the cloacal region to roentgen irradiation was observed, for example, in an animal 49 days after treatment of whole body exclusive of the head with 3,000 r (Fig. 45). According to Domagk,[16] the intestinal canal in the mammals is highly sensitive to roentgen irradiation.

11. *The Spinal Cord*

The central nervous system is resistant to irradiation and usually is completely normal in appearance in the treated animals. Only in rare cases is it possible to find damage in some regions of the spinal cord (8 per cent of all cases). It is surprising that this damage can be comparatively serious and was observed in animals surviving long periods of time after treatment; for example, in animals which died 102 days after irradiation of whole body exclusive of the head with 3,000 r. In this case the usual pattern of spinal cord was completely disorganized. A great hemorrhage occurred in the central region of the spinal cord (Fig. 50). The formation of giant nerve cells in large numbers was observed, which exhibited great differences (Fig. 53) as compared to normal cells of control animals (Fig. 52). This difference can be seen not only in size and shape of the cells but also in the distribution of these cells in the spinal cord. In the irradiated spinal cord, this distribution is completely irregular. It is noteworthy that other regions of the same spinal cord were also irradiated, but had a completely normal appearance (Fig. 51). It is clear that we have different response to irradiation of various regions of the same organ.

Fig. 34–39. 34. Part of the section through the liver of axolotl (No. 67) which died 28 days after total body irradiation with 6,000 r and 75 days after hatching. (LC) Liver cells. Photomicrograph, ×450.

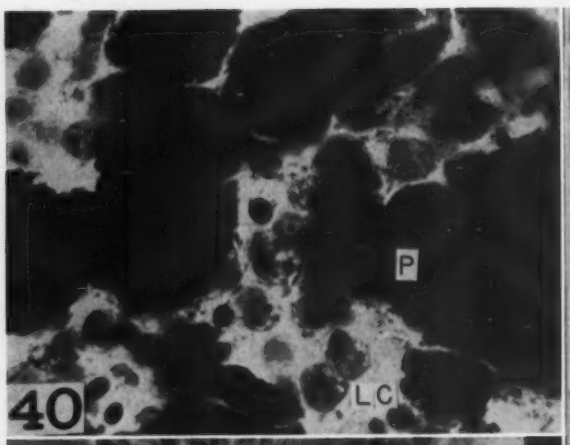
35. Part of the section through the peripheral portion of the liver of control animal 68 days after hatching. (B) Blood vessel; (LC) liver cells; (MT) mitotic figure in lymphatic tissue. Photomicrograph, ×450.

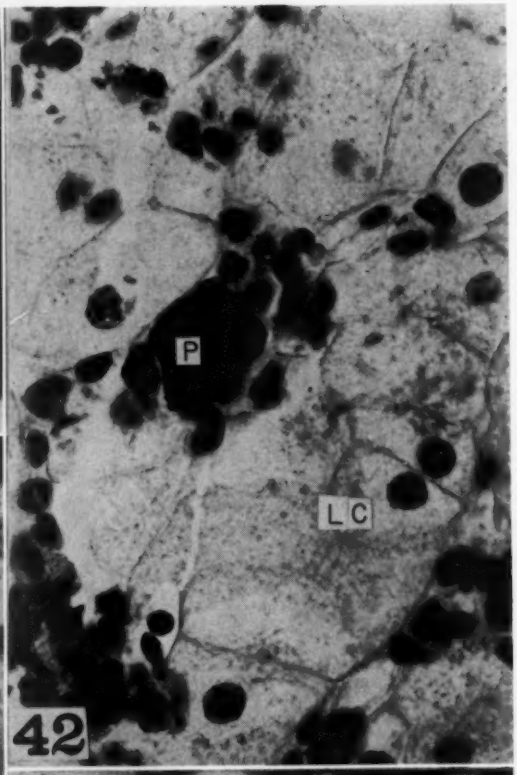
36. Part of the section through the liver of axolotl (No. 64) which died 27 days after total body irradiation with 6,000 r and 72 days after hatching. (B) Blood vessel; (LC) liver cells. Photomicrograph, ×450.

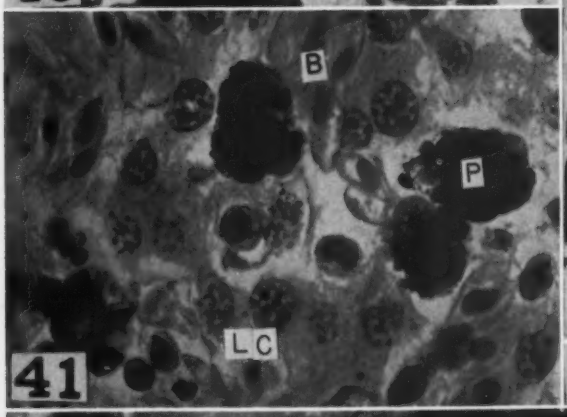
37. Part of the section through the liver of axolotl (No. 54) which died 102 days after irradiation of whole body exclusive of the head with 3,000 r and 133 days after hatching. (LC) Liver cells. Photomicrograph, ×450.

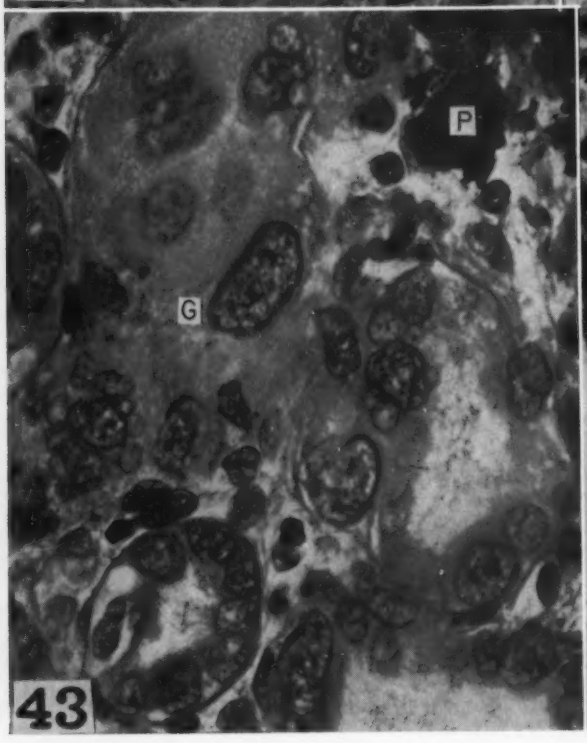
38. Part of the section through the peripheral portion of the liver of control animal (No. 33) 89 days after hatching. (LC) Liver cells; (P) peripheral portion of the liver (lymphatic tissue).Photomicrograph,×450.

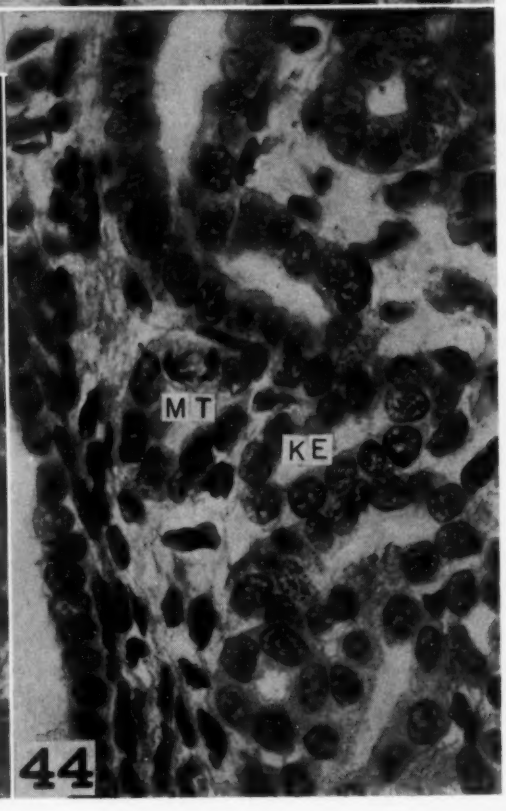
39. Part of the section through the peripheral portion of the liver of axolotl (No. 65) which died 27 days after total body irradiation with 6,000 r and 72 days after hatching. Absence of peripheral lymphatic tissue. (LC) Liver cells. Photomicrograph, ×450.


P
LC
40


P
LC
42


B
P
LC
41


P
G
43


MT
KE
44

12. *The Retina*

Damage to the retina of the eye after total body irradiation was observed in 23 per cent of all animals. This damage never resulted from total body irradiation with 3,000 r but did occur in 50 per cent of the animals treated with 6,000 r. This might be due to a comparatively slow reaction of the retina to irradiation with 3,000 r. Therefore, the animals of this group died before injury to the eye was apparent. The dose of 6,000 r is large enough for the observation of the reaction of the retina soon after treatment. Animals receiving only 3,000 r head irradiation live a comparatively long time and damage to the retina and later disappearance of the eyes and teeth occurred in this study, just as it did in our previous experiments.[9,10,13]

Table I

ALL TYPES OF ROENTGEN DAMAGE OF INVESTIGATED TISSUES AND ORGANS IN PERCENTAGE OF ALL CASES

	Per Cent
1. Spinal cord	8
2. Muscles	15
3. Pigment layer	19
4. Cartilaginous tissue	25
5. Kidney epithelium	35
6. Spleen	56
7. Liver	64
8. Epithelium of skin and the gills	73
9. Epithelium of small intestine	75
10. Loose connective tissue	85
11. Epithelium of cloaca	94
12. Lymph nodes	100

DISCUSSION

The present investigation shows that sensitivity of various tissues and organs to roentgen irradiation is very different. It is seen in Table I that it is possible to observe the lowest sensitivity in the spinal cord and the greatest in lymph nodes and epithelium of cloaca. For evaluation of the damage of tissues or organs leading to the death of animals, the most important to take into consideration are those which exhibit serious roentgen damage. Table II shows that the most severe damage was observed in lymph nodes and connective tissue, epithelium of the skin and gills, epithelium of cloaca, spleen and epithelium of the kidney. Obviously the damage to these tissues and organs caused the death of animals. It was possible to observe different combinations of damage of several tissues and organs in various cases. For illustration of this, we will consider several examples of investigation of dying or dead animals after roentgen irradiation.

No. 13 died 30 days after total body irradiation with 3,000 r, with the following injuries: severe damage of lymph nodes, loose connective tissue, and epithelium of the skin, and with medium or slight damage of spleen, small intestine and cloacal epithelium.

No. 51 fixation was made on a dying animal 49 days after irradiation of the whole body exclusive of the head with 3,000 r. There was severe damage of loose connective tissue, epithelium of small intestine and cloaca, and slight damage of kidney, liver and cartilaginous tissue.

Fig. 40–44. 40. Part of the section through the liver of axolotl (No. 15) 158 days after irradiation of the head with 3,000 r and 190 days after hatching. (LC) Liver cells; (P) pigment cells. Photomicrograph, ×450.

41. Part of the section through the liver of axolotl (No. 19) 92 days after irradiation of the head with 3,000 r and 123 days after hatching. (B) Blood vessel; (LC) liver cells; (P) pigment cell. Photomicrograph, ×450.

42. Part of the section through the liver of control animal (No. 36) 169 days after hatching. (LC) Liver cells; (P) pigment cell. Photomicrograph, ×450.

43. Part of the section through the kidney of axolotl (No. 54) 102 days after irradiation of whole body exclusive of the head with 3,000 r and 133 days after hatching. (G) Giant cell; (P) pigment cell. Photomicrograph, ×450.

44. Part of the section through the kidney of control animal 68 days after hatching. (MT) Mitotic figure; (KE) kidney epithelium. Photomicrograph, ×450.

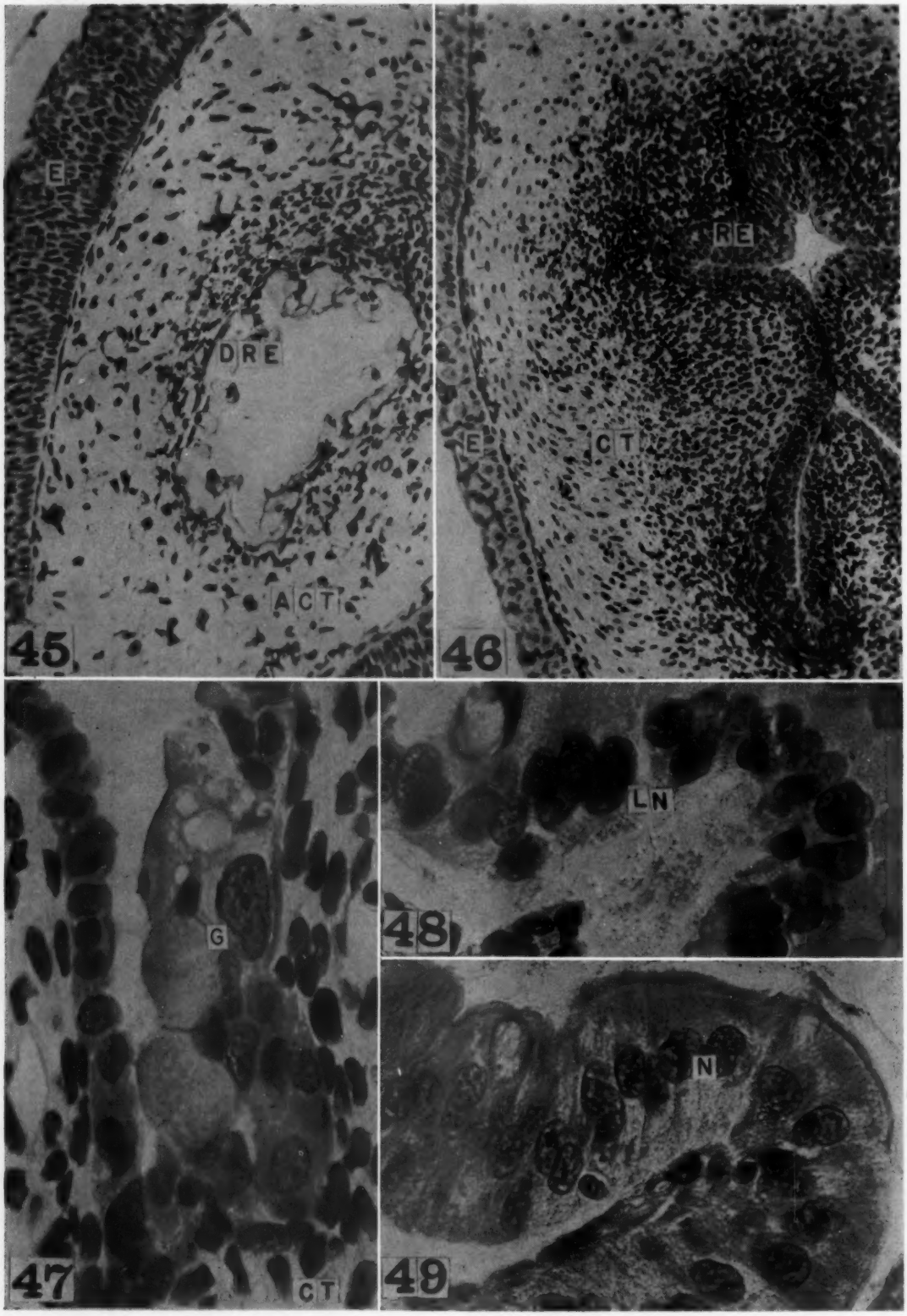

E
DRE
ACT
45
RE
E
CT
46
G
47
CT
LN
48
N
49

Table II

SERIOUS ROENTGEN DAMAGE OF INVESTIGATED TISSUES AND ORGANS IN PERCENTAGE OF ALL CASES

	Per Cent
1. Spinal cord	4
2. Cartilaginous tissue	4
3. Liver	8
4. Epithelium of small intestine	11
5. Kidney epithelium	15
6. Spleen	19
7. Epithelium of cloaca	35
8. Epithelium of skin and the gills	46
9. Loose connective tissue	73
10. Lymph nodes	100

No. 54 died 102 days after irradiation of the whole body exclusive of the head with 3,000 r. There was severe damage of kidney epithelium and spinal cord and slight damage of loose connective tissue and cloacal epithelium.

No. 67 died 28 days after total body irradiation with 6,000 r. There was severe damage of lymph nodes, loose connective tissue, epithelium of small intestine and cloaca, and slight damage of spleen, kidney, liver, epithelium of the skin and cartilaginous tissue.

Associated with the death of animals during primary acute reaction, probably the damage of epithelium of skin and gills is very important because they are both very essential for the normal respiratory metabolism of these animals. For animals surviving long periods of time, the damage of kidney epithelium as a cause of death probably is important.

It is necessary to emphasize that according to our observations, the complete damage of an entire organ (for example, the liver) or a tissue (for example, the skin epithelium) was observed in comparatively few cases. But even in such cases, there never was 100 per cent injury of all cells. Near the damaged cells it was always possible to find cells which were normal in appearance. This is in accordance with the statement of Warren[31] that tremendous doses are required to kill all cells in the tissue, although slight doses will kill some. In most cases, even in the animals after total body irradiation with the lethal dosage, definite damage can be observed only in some regions of a tissue or organ while other regions (also irradiated) are normal in appearance. For example, in one region of skin epithelium of an animal after total body irradiation, it is possible to see the typical degenerating giant cells, but other regions of the epithelium of the same animal are normal in appearance. It was mentioned that in the spinal cord definite damage was restricted to one region, but other regions of the same spinal cord (also irradiated) were completely normal. A significant difference exists in the reaction to irradiation with the same dosage between local and total body irradiation.

Obviously the roentgen damage cannot always be visible. According to our previous observations,[5] the appearance of all tissues during the secondary stable state was normal in spite of complete suppression of mitotic activity. Bloom[2,3] also distinguished between "visible changes in

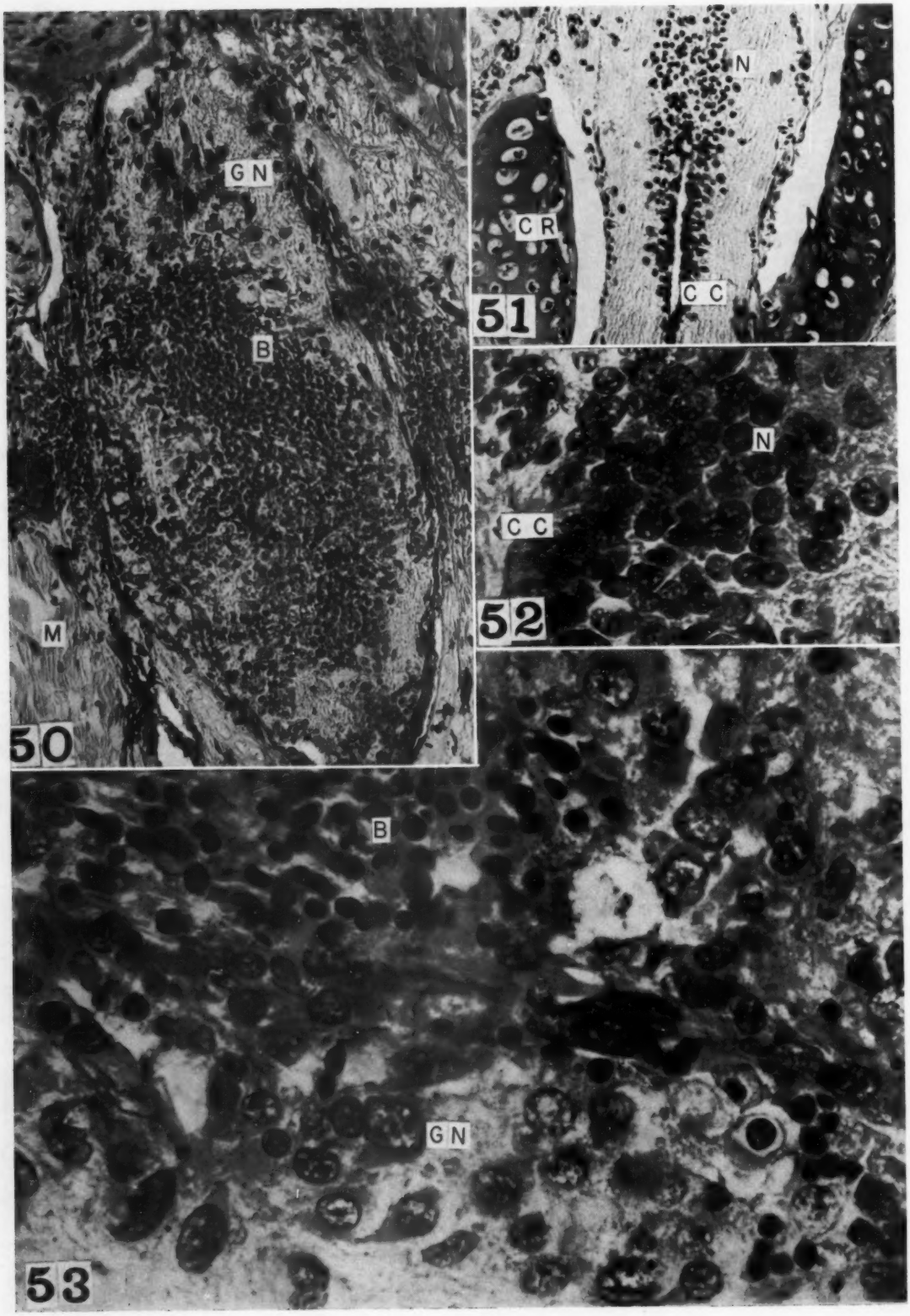
Fig. 45–49. 45. Part of the section through the body of axolotl (No. 51) 49 days after irradiation of whole body exclusive of the head with 3,000 r and 81 days after hatching. Cloacal region. (ACT) Abnormal connective tissue; (DRE) degenerating cloacal epithelium; (E) skin epithelium. Photomicrograph, ×450.

46. Part of the section through the body of control animal 68 days after hatching. Cloacal region. (CT) Loose connective tissue; (E) skin epithelium; (RE) cloacal epithelium. Photomicrograph, ×450.

47. Part of the section through the body of axolotl (No. 47) 39 days after hatching. Cloacal region. (CT) Enlarged connective tissue cells; (G) giant cell in cloacal epithelium. Photomicrograph, ×450.

48. Part of the section through the intestine of axolotl (No. 67) which died 28 days after total body irradiation with 6,000 r and 75 days after hatching. (LN) Enlarged nuclei of intestine epithelium. Photomicrograph, ×450.

49. Part of the section through the intestine of control animal (No. 33) 89 days after hatching. (N) Nuclei of intestine epithelium. Photomicrograph, ×450.


GN
B
M
50
N
CR
CC
51
N
CC
52
B
GN
53

cells" and "invisible changes" after irradiation. According to Bloom, "In general, I would say that we found no histologic evidence for the cause of death following irradiation. That is, we could see no differences between the animals which died with an LD 50/30 days dose and those which did not die after the same dose" (p. 345).

It was mentioned that in spite of total body irradiation, very often only partial damage of tissue or the organ resulted. It is noteworthy that in many cases in such organs as liver or spleen, in spite of irradiation, not only normal appearance of cells but also great mitotic activity was observed. It is interesting that such activity occurred even in the dying animals after irradiation with 6,000 r. For example, animal No. 77: fixation of dying animal was made 26 days after irradiation with 6,000 r of the whole body exclusive of the head. Severe damage of loose connective tissue, epithelium of the skin (Fig. 54), small intestine and cloaca was seen. Slight damage of spleen and cartilaginous tissue also was noted. In this animal it was possible to see isolated mitotic figures in the liver (Fig. 55). In the spleen, in spite of signs of damage and abnormally large size (Fig. 28), many mitotic figures were present. This was also true of the spleen of animal No. 51 (Fig. 57 and 58) with severe damage of loose connective tissue and epithelium of small intestine and cloaca. Thus, roentgen irradiation with lethal doses in one region of the organism inhibits mitotic activity and destroys the tissue. In other regions of the same organism, mitotic activity is stimulated. The count of mitotic figures in 12 sections of normal animals showed that variations are very great, from 5 mitotic figures in one section to 68 mitotic figures in another section, with a mean of 29. The count of mitotic figures in an irradiated spleen (Fig. 56) with unusual mitotic activity showed a variation in the number of mitotic figures from 20 to 63 in one section, with a mean of 37.6. The unusually large mitotic activity in irradiated spleen is evident. We consider this observation as a new evidence of roentgen stimulation.

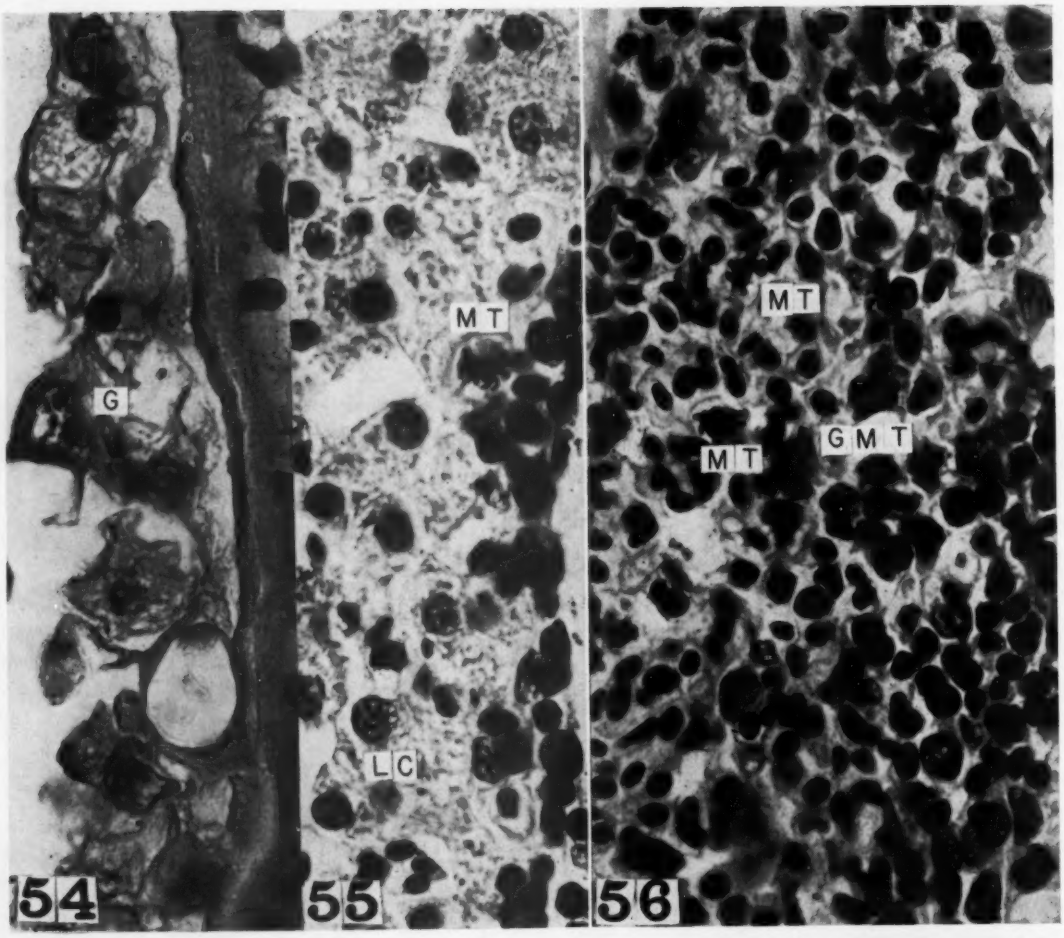
This phenomenon was the subject of our article in this JOURNAL a few years ago.[7] This article was criticized by Rugh.[28] According to this author, "Clinically, there is no evidence of any stimulating effect of ionizing radiations. It can hardly be said that edema, erythema, or hemorrhage is evidence of radiation stimulation" (p. 48). Roentgen cancer was considered as clinical evidence of roentgen stimulation. Of course, it is questionable whether the stimulating and cancerogenic effects of roentgen irradiation are the same. The relation between these two effects has not been investigated, but it is possible that a close relationship exists. Many authors observed the cancerogenic effect of roentgen irradiation under experimental conditions. For example, Kaplan[22] reported that malignant changes may occur many months or even years after treatment, following necrosis in an overirradiated skin area. Furth[18] and Furth and Boon[19] observed that following irradiation of 4 to 6 weeks old mice with 87–350 r, ovarian tumors began to appear when the mice were about 11 months of age. The frequency of these neoplasms in-

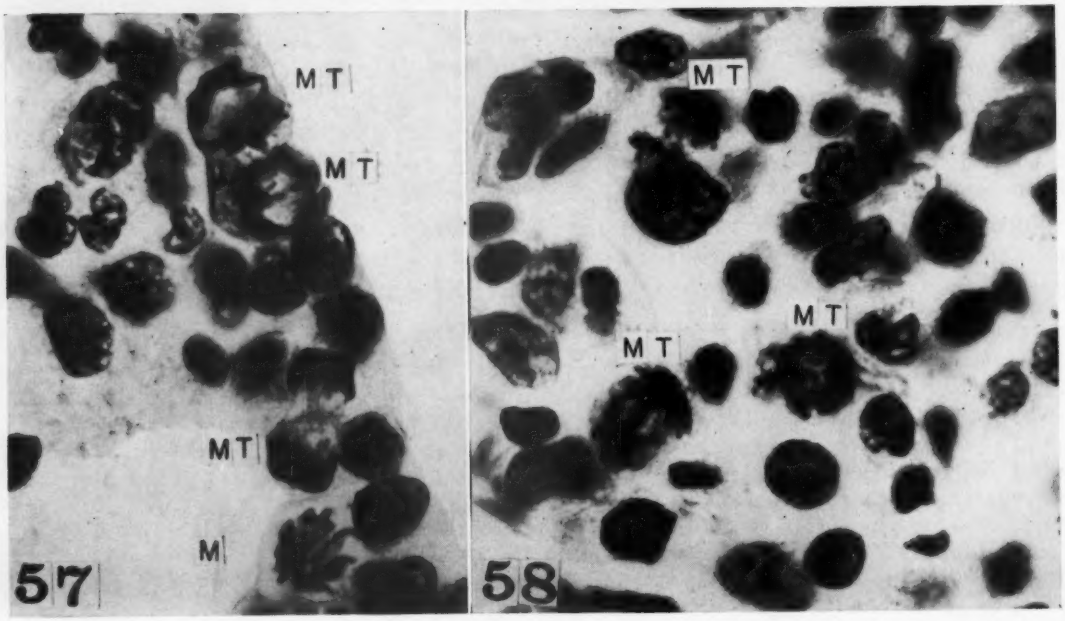
FIG. 50–53. 50. Part of the section through the body of axolotl (No. 54) which died 102 days after irradiation of whole body exclusive of the head with 3,000 r and 133 days after hatching. (B) Hemorrhage inside of the spinal cord; (GN) giant nerve cells; (M) muscles. Photomicrograph, ×100.

51. Part of the section through the body of the axolotl (No. 54; see Fig. 50). Another section of spinal cord, which is normal in appearance. (CC) Central canal; (CR) cartilage; (N) nerve cells, which are normal in appearance. Photomicrograph, ×100.

52. Part of the section through the spinal cord of control animal (No. 33) 89 days after hatching. (CC) Central canal; (N) nerve cells. Photomicrograph, ×450.

53. Part of the section through the spinal cord of the animal shown (No. 54; see Fig. 50). (B) Hemorrhage inside the spinal cord; (GN) giant nerve cell. Photomicrograph, ×450.


G
MT
LC
MT
MT
GMT
54
55
56


MT
MT
MT
M
MT
MT
MT
57
58

creased with time and almost every mouse that lived 17 months developed an ovarian tumor. The induced tumors were usually complex, granulosa cell tumors, luteomas, glandular tumors, and other types. Koletsky and Gustafson[24] described, in a series of rats which survived a single dose of 660 r of whole body irradiation, an unusually high incidence of neoplasms. The animals developed a wide variety of tumors, both benign and malignant, especially in the skin and subcutaneous tissues and also in the viscera.

It is clear that in roentgen irradiation in a laboratory experiment, we have a factor that can produce, by some conditions, a great acceleration of mitotic activity and as a result of this the development of a new organ (stimulating effect) or tumor (cancerogenic effect). In some cases, as a result of stimulation, new organs do not always develop, but only abnormal outgrowths. It is very possible that the difference between stimulating and cancerogenic effects does not exist and that the distinction between them is artificial but this is the problem for future investigation.

It is noteworthy that we have some new evidence of the existence of roentgen stimulation which was received after publication of an earlier article.[7] In irradiated tails of Rana catesbiana tadpoles, unusually large epithelial outgrowths in the shape of long strips or layers were observed between the portions of degenerating giant cell epithelium in distal regions and in all proximal region formations. The cells of these outgrowths were normal in size. It was observed that these formations were developed as the result of intensive mitotic activity. It was noted that development of these epithelial strips was observed in some places in close proximity to the typical degenerating giant cell epithelium. This development can be explained by the formation of some disintegration products ("necrohormones") in the giant cell degenerating epithelium. These products may stimulate the mitotic activity in the neighboring region of epithelium.[11]

If we try to summarize all our previous results concerning the problem of roentgen stimulation and new observations that we have in the present material, we may come to the following conclusions:

1. It is obvious that the ability to divide is not always suppressed by irradiation in all cells, in spite of treatment with large doses of roentgen rays.

2. Under some conditions, the mitotic activity can be stimulated by irradiation. This can be observed in the peripheral zone of the irradiated field in experiments with local irradiation or in some internal organs (spleen or liver) in experiments with total body irradiation.

3. Probably the secondary stimulation is the result of the action of disintegration products ("necrohormones").

It was mentioned that primary acute reaction was observed after total body irradiation and after the irradiation of the body exclusive of the head, but it is necessary to note that significant differences were seen between reactions to irradiations described in this paper and reactions after local ir-

Fig. 54–58. 54. Part of the section through the body of dying axolotl (No. 77, the last surviving animal in experiment) 26 days after irradiation of whole body exclusive of the head with 6,000 r and 73 days after hatching. (G) Giant cell degenerating epithelium. Photomicrograph, ×450.

55. Part of the section through the liver of the axolotl (No. 77; see Fig. 54). (MT) Mitotic figure; (LC) liver cells. Photomicrograph, ×450.

56. Part of the section through the spleen of the axolotl (No. 77; see Fig. 54). (GMT) Group of mitotic figures; (MT) mitotic figure. Photomicrograph, ×450.

57. Part of the section through the spleen of axolotl (No. 51) 49 days after irradiation of whole body exclusive of the head with 3,000 r and 81 days after hatching. (MT) Mitotic figure. Photomicrograph, ×900.

58. Part of the section through the spleen of the axolotl (No. 51; see Fig. 57). (MT) Mitotic figure. Photomicrograph, ×900.

radiation of the extremity or tail of axolotls. According to our previous papers,[4,12] after local irradiation the primary acute reaction was always observed between 20 and 60 days following treatment. This reaction is characterized by formation of giant cell degenerating epithelium, reduction of subcutaneous pigment layer, presence of macrophages, signs of inflammation, suppression of mitotic activity and, in some cases, by "zone of stimulation." Tissues become normal in appearance after the end of the primary acute reaction approximately 60 or more days after local irradiation. In the present material, epithelium normal in appearance was found in some cases as early as 39 days after treatment, and definite damage resulted in some tissues or organs after the primary acute reaction subsided. This reaction in itself has shown some peculiarities in the present material. For example, the reduction of the pigment layer did not occur. Macrophages were observed only in some cases and the accumulation of large numbers of small cells in the "zone of stimulation" could not be found after total body irradiation, since they are either a response of some untreated region of the body to the effect of the locally irradiated area or a phenomenon that can be observed only in the boundary region between the irradiated and the nonirradiated part of the body. But we have no explanation why the reduction of the pigment layer was not observed in this material. According to our previous observations, all elements of the primary acute reaction do not always occur after local irradiation. For example, the reduction of pigment layer was not observed after local irradiation of the jaws of the axolotl.[13] Degenerating giant cell epithelium appeared in the irradiated region of the tail in experiments one year,[4] but in another year it was absent in a repetition of the same experiments although the material and conditions were presumably the same. The degenerating giant cell epithelium was not seen after irradiation of the head of axolotl,[9] while it was clearly seen after irradiation of the jaws in other experiments with the same species.[13] Our knowledge of tissue reactions to irradiation is limited and investigation of this problem must be continued.

It is interesting to compare our data concerning histopathology of roentgen death of axolotl with similar data of various investigators concerning the roentgen death in mammals. Table III shows such comparison. According to all investigators, the lymph nodes are most sensitive to irradiation, and according to almost all investigators, the nervous system is the most resistant. Only Henshaw and Snider[21] consider the muscles as the most resistant tissue; most other authors feel that the muscles are second to the nervous system. It is unusual that the spleen in axolotl is much more radioresistant than the lymph nodes. According to Schlumberger and Vasquer[30] in mammals, "The changes in the lymph nodes paralleled those found in the spleen" (p. 1020), but on the other hand, according to Bloom and Bloom,[3] changes in environment affect the response of the cell to irradiation. For example, the greater sensitivity of lymphocytes in lymph nodes compared to those located in the lamina propria was observed. It is possible that in the spleen of axolotl, there are some environmental conditions which make the lymphocytes much more resistant than those in lymph nodes. It is necessary to take into consideration that in axolotl, the blood forming organs have some peculiarities. One of the most important organs of this system, the bone marrow, does not exist in axolotl. It was mentioned that the peripheral portion of the liver is a lymphatic organ and plays an important role in blood forming process. It is possible that the spleen also may have some peculiarities in structure or in physiologic activity that are important for radiosensitivity of this organ. Hartmann[20] emphasized that blood forming organs in Amphibia are quite different from such organs in higher vertebrates, and Kendall[23] noted that the peripheral portion of the liver in Amphibia is a blood forming organ. Special attention must be given

TABLE III

THE COMPARISON OF SENSITIVITY OF VARIOUS TISSUES AND ORGANS ACCORDING TO OUR DATA IN AXOLOTL AND ACCORDING TO OTHER AUTHORS* IN MAMMALS ARRANGED ACCORDING TO A PROGRESSIVE INCREASE IN SENSITIVITY

Our Data	Desjardins[15] (1932)	Warren[31] (1944)	Henshaw and Snider[21] (1946)	Schlumberger and Vasquez[30] (1954)
1. Spinal cord	Nerve cells	Neuron	Muscles	Nervous system
2. Muscles	Muscle cells	Fibroblast	Brain and nerve	Muscles
3. Pigment layer	Connective tissue cells	Muscle cells	Kidney	Kidney and liver
4. Cartilaginous tissue	Epithelial cells	Epithelial cells	Liver	Gastrointestinal tract
5. Kidney epithelium	Lymphoid cells	Lymphocytes	Connective tissues	Spleen
6. Spleen			Skin	Lymph nodes
7. Liver			Gastrointestinal epithelium	
8. Epithelium of skin			Lymph nodes	
9. Epithelium of small intestine				
10. Loose connective tissue				
11. Epithelium of cloaca				
12. Lymph nodes				

* In this table we take only such data of other authors that can be compared with our data. We do not investigate gonads and therefore we do not take the data of other authors concerning the sensitivity of gonads.

to the fact that loose connective tissue (fibroblasts) in our material is much more sensitive to irradiation than in mammals. It is necessary to take into consideration that even in the cases when the damage to this tissue is considered as serious, we never observed the damage of all fibroblasts of the irradiated region. On the contrary, most regions of this tissue were normal in the appearance, but in some places we have seen the formation of giant cells in great number. It is very interesting that Maximow[25] observed the formation of giant fibroblasts in the rabbit after roentgen irradiation. According to this author, "the hypertrophy of the fibroblasts has now become very marked. . . . With their strongly basophilic, flat, giant cell bodies and their numerous processes running in different directions and often branching, they resemble large nerve cells. The nuclei, mostly oval or kidney-shaped, and occupying an eccentric position, have attained a quite excessive size. Their interior is filled with numerous coarse, darkly-stained chromatic granules partly covering the nucleoli, and sometimes contains large intra-nuclear vacuoles" (p. 328). From this citation, it is clear that Maximow observed giant fibroblasts which are very similar to those seen in axolotl. According to Bloom and Bloom,[3] "The adipose, pigment, tendonous and mucous connective tissues have not been studied sufficiently for radiation effects" (p. 1097). This may be a possible explanation of described difference in sensitivity of loose connective tissue.

If we take into consideration this explanation concerning sensitivity of connective tissue, we may conclude that this investigation showed that, despite the fact that urodele amphibians (axolotl) are very far apart from mammals in their phylogenetic origin, the effects of roentgen rays upon these two groups are similar.

SUMMARY

1. The histopathology of roentgen death after total body and partial irradiation is considered.

2. Damage of epithelium was observed in 85 per cent of all animals fixed during the

primary acute reaction to irradiation (between 20 and 60 days after treatment). The typical damage is formation of giant cell degenerating epithelium.

3. Partial damage of loose connective tissue was seen in 85 per cent of all cases, represented by the formation of giant fibroblasts.

4. Definite damage of cartilaginous tissue occurred in only 25 per cent of all cases. Many abnormalities in nuclei (multinucleation, fragmentation) were seen.

5. Damage of muscles was noted only in 15 per cent of all cases. (The nuclei were larger than usual.)

6. Damage of spleen appeared in 56 per cent of all cases. In such cases, the number of lymphocytes was greatly reduced and the presence of unusually large cells with granulated protoplasm was typical.

7. After total body irradiation, the serious damage of lymph nodes was observed in 100 per cent of the cases. In 75 per cent of all cases, they disappeared completely.

8. Damage of liver was seen in 69 per cent of all cases, but only in 8 per cent of the cases this damage can be evaluated as serious.

9. Damage of kidney was observed in 35 per cent of the cases and in 15 per cent of all cases the formation of giant cells in kidney epithelium was observed (serious damage).

10. Damage of small intestine was seen in 75 per cent of the cases, but only in 11 per cent of all cases was this damage considered serious. The cloacal region is much more sensitive. Damage was observed in 94 per cent of the cases and in 35 per cent of all cases this damage was serious.

11. The spinal cord is very resistant to irradiation. In only 8 per cent of the cases was damage observed.

12. In many cases it was possible to see different combinations of damage of several tissues and organs, which were probably the cause of roentgen death.

13. Complete damage of an entire organ or tissue was observed only in rare instances. In most cases, even in the animals after total body irradiation with the lethal dosage, damage was seen only in some regions of a tissue or organ while other regions (also irradiated) were normal in appearance.

14. Great mitotic activity was observed in the liver and spleen in even dying animals after total body irradiation. We consider this observation as a new evidence of roentgen stimulation. This problem is discussed in this paper.

15. The primary acute reaction, which was described after total irradiation, can be observed also after total body irradiation and after irradiation of the body exclusive of the head, but with great modifications.

16. The data concerning histopathology of roentgen death of axolotl are compared with similar data of various investigators concerning roentgen death of mammals.

17. Despite the fact that urodele amphibians (axolotl) are very far apart from mammals in their phylogenetic origin, the histopathology of roentgen death in these two groups is similar.

Roswell Park Memorial Institute
Buffalo 3, New York

The author wishes to express his appreciation to Mr. Fred Bock of Roswell Park Memorial Institute for his assistance during the preparation of this manuscript and to Dr. R. R. Humphrey of the University of Buffalo, School of Medicine, for axolotl eggs. The author wishes also to express his appreciation to Miss Lidia Bolotoff and Mrs. Alla Sigarew for preparation of the slides and Mrs. Nadia Schmigelsky for the care of experimental animals.

REFERENCES

1. BLOOM, W. Histological changes following radiation exposures. *Radiology*, 1947, *49*, 344–347.
2. BLOOM, W. Histopathology of Irradiation from External and Internal Sources. McGraw-Hill Book Company, Inc., New York, 1948, pp. 1–808.
3. BLOOM, W., and BLOOM, M. A. Histological Changes after Irradiation. Radiation Biology, I. Part II. McGraw-Hill Book Company, Inc., New York, 1954, pp. 1091–1143.
4. BRUNST, V. V. Effect of local x-ray irradiation on

tail development of young axolotl. *J. Morphol.*, 1950, *86*, 115–151.

5. Brunst, V. V. Influence of x-rays on limb regeneration in urodele amphibians. *Quart. Rev. Biol.*, 1950, *25*, 1–29.
6. Brunst, V. V. Technics of local low voltage roentgen ray irradiation of experimental animals. *Laborat. Inves.*, 1952, *1*, 432–438.
7. Brunst, V. V. Problem of roentgen stimulation. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1952, *68*, 281–289.
8. Brunst, V. V. Comparison of effects of local roentgen irradiation on jaws and tooth development in young axolotls and mice. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1954, *72*, 488–497.
9. Brunst, V. V. Effect of local x-ray irradiation upon development of anterior part of head of axolotl. *J. Morphol.*, 1954, *95*, 373–392.
10. Brunst, V. V. Influence of roentgen irradiation on development of eye of axolotl. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1955, *73*, 281–293.
11. Brunst, V. V. Reaction of skin epithelium of tails of Rana catesbiana tadpoles to local x-irradiation. *Radiation Research*, 1955, *2*, 556–567.
12. Brunst, V. V., Barnett, D. J., and Figge, F. H. J. Reaction of tissues of amphibians after local roentgen irradiation. Am. J. Roentgenol. & Rad. Therapy, 1951, *66*, 420–434.
13. Brunst, V. V., Sheremetieva-Brunst, E. A., and Figge, F. H. J. Effect of local x-ray irradiation upon teeth and surrounding tissues in young axolotls. *J. Dent. Res.*, 1952, *31*, 601–619.
14. Brunst, V. V., Sheremetieva-Brunst, E. A., and Figge, F. H. J. Comparison of reactions of irradiated parts of bodies of two day old mice and urodele amphibians to roentgen treatment. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., 1953, *70*, 283–293.
15. Desjardins, A. U. Radiosensitiveness of cells and tissues and some medical implications. *Science*, 1932, *75*, 569–575.
16. Domagk, G. Gewebsveränderungen nach Röntgenbestrahlungen. *Ergebn. im Med.*, 1928, *33*, 1–62.
17. Ewing, T. Tissues reactions to radiation. Am. J. Roentgenol. & Rad. Therapy, 1926, *15*, 93–115.
18. Furth, J. Factors of induction of ovarian tumors by x-rays: Types, character and histogenesis of these growths. Fourth Internat. Cancer Res. Congress, St. Louis, 1947, p. 117.
19. Furth, J., and Boon, M. C. Induction of ovarian tumors in mice by x-rays. *Cancer Research*, 1947, *7*, 241–245.
20. Hartmann, A. Über die Einwirkung von Röntgenstrahlen auf Amphibienlarven. Einwirkung geringer Strahlendosen auf das Blut und das blutbildende Gewebe von Rana temporaria Larven. *Arch. f. Entwicklungsmechn. d. Organ.*, 1921, *47*, 131–209.
21. Henshaw, P. S., and Snider, R. S. Correlation of tissue responses following exposure to penetrating radiations. M.D.D.C. (U.S.A.E.C.) 1946, 569.
22. Kaplan, I. I. Sarcoma of cheek following Tricho x-ray treatment for hair on face. *J.A.M.A.*, 1934, *102*, 595–597.
23. Kendall, J. I. Microscopic Anatomy of Vertebrates. Lea & Febiger, Philadelphia, 1949.
24. Koletsky, S., and Gustafson, G. E. Whole-body radiation as carcinogenic agent. *Cancer Research*, 1955, *15*, 100–104.
25. Maximow, A. A. Studies on changes produced by roentgen rays in inflamed connective tissue. *J. Exper. Med.*, 1923, *37*, 319–340.
26. Rugh, R. Histological effects on embryo following x-irradiation. *J. Morphol.*, 1949, *85*, 483–501.
27. Rugh, R., Levy, B., and Sapadin, L. Histopathological effects of immediate and delayed radiation death in hamsters produced by two million volt x-rays. I. Lymphocytic organs: spleen, lymph nodes, thymus and bone marrow. *J. Morphol.*, 1952, *91*, 237–267.
28. Rugh, R. Effect of ionizing radiations on amphibian development. *J. Cell. & Comp. Physiol.*, 1954, *43*, 39–76.
29. Scheremetiewa, E. A., and Brunst, V. V. Untersuchung des Einflusses von Röntgenstrahlen auf die Regeneration des Schwanzes bei den Kaulquappen von Pelobates fuscus. *Arch. f. Entwicklungsmechn. d. Organ.*, 1933, *130*, 771–791.
30. Schlumberger, H., and Vasquez, T. T. Pathology of total body irradiation in monkey. *Am. J. Path.*, 1954, *30*, 1013–1047.
31. Warren, S. Histopathology of radiation lesions. *Physiol. Rev.*, 1944, *24*, 225–238.

THE AMERICAN JOURNAL OF ROENTGENOLOGY, RADIUM THERAPY AND NUCLEAR MEDICINE

Editor: LAWRENCE REYNOLDS, M.D.

Associate Editors: HARRY HAUSER, M.D., TRAIAN LEUCUTIA, M.D., RUSSELL H. MORGAN, M.D., EDWARD B. D. NEUHAUSER, M.D., WENDELL G. SCOTT, M.D.

Consulting Editorial Board: See front cover.

Published by: CHARLES C THOMAS, PUBLISHER, 301–327 East Lawrence Avenue, Springfield, Illinois.

Issued monthly. Annual subscription: United States, Mexico, Cuba, Central and South America, $15.00; Canada, $16.00; other countries, $17.00. Current single numbers, $1.50. Advertising rates submitted on application. Editorial office, 110 Professional Building, Detroit 1, Michigan. Office of publication, 301–327 East Lawrence Avenue, Springfield, Illinois. Information of interest to authors and readers will be found on page vi.

Officers and Standing Committees

AMERICAN ROENTGEN RAY SOCIETY

President: W. Edward Chamberlain, Philadelphia Pa.; *President-Elect:* Wendell G. Scott, Clayton, Mo.; *1st Vice-President:* Vincent W. Archer, Charlottesville, Va.; *2nd Vice-President:* Philip J. Hodes, Philadelphia, Pa.; *Secretary:* Barton R. Young, Germantown Hospital, Philadelphia 44, Pa.; *Treasurer:* Robert K. Arbuckle, Samuel Merritt Hospital, Hawthorne and Webster Sts., Oakland 9, Calif.

Executive Council: W. E. Chamberlain, W. G. Scott, V. W. Archer, B. R. Young, R. K. Arbuckle, Lawrence Reynolds, E. L. Jenkinson, H. B. Elkins, J. F. Holt, P. C. Hodges, J. C. Dickinson, J. C. Cook, R. M. Caulk, C. A. Good, A. E. Childe, Wilbur Bailey, E. B. D. Neuhauser, Chairman, 300 Longwood Ave., Boston, Mass.

Program Committee: B. R. Young, Philadelphia, Pa., H. B. Elkins, Iowa City, Iowa, Lawrence Reynolds, Detroit, Mich., J. F. Holt, Ann Arbor, Mich., E. B. D. Neuhauser, Boston, Mass., H. O. Peterson, St. Paul, Minn., Wendell G. Scott, Chairman, Clayton, Mo.

Publication Committee: H. G. Reineke, Cincinnati, Ohio, V. P. Collins, Houston, Texas, J. F. Roach, Albany, N. Y., H. M. Stauffer, Philadelphia, Pa., Higdon B. Elkins, Chairman, Iowa City, Iowa.

Finance and Budget Committee: Wilbur Bailey, Los Angeles, Calif., A. E. Childe, Winnipeg, Manitoba, L. W. Paul, Madison, Wis., J. E. Miller, Dallas, Texas, Edward L. Jenkinson, Chairman, Chicago, Ill.

Committee on Scientific Exhibits: R. H. Marshak, New York, N. Y., Cesare Gianturco, Urbana, Ill., John F. Holt, Chairman, Ann Arbor, Mich.

Representative on American Board of Radiology: H. D. Kerr, St. Michaels, Md., T. Leucutia, Detroit, Mich.

Director of Instructional Courses: H. O. Peterson, St. Paul, Minn., *Manager of Annual Meeting:* James C. Cook, 110 Professional Building, Detroit 1, Mich.

Editor: Lawrence Reynolds, 110 Professional Building, Detroit 1, Mich.

Fifty-eighth Annual Meeting: Shoreham Hotel, Washington, D. C., October 1–4, 1957.

AMERICAN RADIUM SOCIETY

President: Ralph T. Ogden, Hartford, Conn.; *President-Elect:* Milford D. Schulz, Boston, Mass.; *1st Vice-President:* Ralph M. Caulk, Washington, D. C.; *2nd Vice-President:* Elizabeth F. Focht, New York, N. Y.; *Secretary:* Theodore R. Miller, 139 East 36th St., New York 16, N. Y.; *Treasurer:* Jesshill Love, St. Joseph Infirmary, Louisville, Ky.

Executive Committee: John E. Wirth, Chairman, Pasadena, Calif.; Grant H. Beckstrand, Long Beach, Calif.; Norman A. McCormick, Windsor, Ontario, Canada.

Program Committee: Ralph T. Ogden, Chairman, Hartford, Conn.; Franklin L. Payne, Philadelphia, Pa.; William S. MacComb, Houston, Texas; John L. Pool, New York, N. Y.; Donald S. Childs, Jr., Rochester, Minn.; Edith H. Quimby, New York, N. Y.; Milford D. Schulz (ex officio), Boston, Mass.

Publication Committee: Harry Hauser, Chairman, Cleveland, Ohio; Martin Van Herik, Rochester, Minn.; J. Robert Andrews, Bethesda, Md.

Public Relations Committee: J. Samuel Binkley, Chairman, Oklahoma City, Okla.; Ernest H. Wood, Chapel Hill, N. C.; Frederick W. O'Brien, Jr., Worcester, Mass.

Janeway Lecture Committee: Gioacchino Failla, Chairman, New York, N. Y.; H. Dabney Kerr, St. Michaels, Md.; Lloyd F. Craver, New York, N. Y.

Representatives on the American Board of Radiology: Douglas Quick, New York, N. Y.; B. P. Widmann, Philadelphia, Pa.; Frederick W. O'Brien, Boston, Mass.

Representatives on National Committee on Radiation Protection: Edith H. Quimby, New York, N. Y.; Theodore P. Eberhard, Ann Arbor, Mich.

Representative on the Board of Chancellors of the American College of Radiology: Charles L. Martin, Dallas, Texas.

Committee on Arrangements: Robert L. Brown, Chairman, Emory University, Ga.; Jesshill Love, Vice-Chairman, Louisville, Ky.; Wade S. Rizk, Jacksonville, Fla; Herbert D. Kerman, Daytona Beach, Fla.; J. Samuel Binkley, Oklahoma City, Okla.; Ralph T. Ogden, Hartford, Conn.

Fortieth Annual Meeting: Hollywood Beach Hotel, Hollywood Beach, Florida, March 27–29, 1958.

EDITORIAL

LEAD POISONING DURING INFANCY AND EARLY CHILDHOOD

THE existence of a few sizable hiatuses does not detract from the statement that the physician of 1957 has sufficient knowledge to diagnose accurately and treat successfully most children or infants with lead poisoning. He has a clear understanding of the epidemiologic and preventive aspects of plumbism while receiving full cooperation from government, industry, and health agencies toward elimination of what, in the past, was a major hazard to child well-being.

The events contributing to this satisfactory state cumulated so rapidly—as events tend to do in present day medicine—that it is difficult to recall but three decades ago when major clinics were only awakening to the extent of the problem and little was offered the patient beyond the advice that sources of lead be avoided—this at a time when Ruddock[1] observed, "A child lives in a lead world."

The dangers of working with lead have been vaguely understood for a number of centuries and most of the occupational and environmental hazards, as well as the clinical aberrations of the victims, were systematically documented over one hundred years ago. Children were considered chiefly as they shared problems with their elders and in certain theoretic considerations of fetal poisoning until some forty years ago when personalized risks of the younger group received attention—the extraction of lead by milk offered in metallic nursing bottles, the application of ointments to the maternal breast, and the coloring of candies and cookies with lead pigments.

Why concise data on plumbism in the younger age group were so slow in crystallizing can be clarified by reading some of the early case reports. First was a paucity of diagnostic aids from either the laboratory or the actual examination. Even that favorite of teachers of Physical Diagnosis, the lead line of Burton, was absent since it seldom develops around deciduous teeth. Stippling had been associated with saturnism since around 1900 but blood smears were done with much less frequency then than today. The physician was thus left with the acumen developed through experience plus his individual tenacity for uncovering a source for poisoning. A second retarding factor was undoubtedly the variation in clinical manifestations of lead poisoning at different stages of life. It is understood now that the small child can ingest appreciable amounts of lead without dramatic clinical manifestations until a second element, usually sunlight, is introduced.[2] Then absorption is accelerated, and quite possibly certain metabolic responses are altered, so that acute toxicity with attendant meningoencephalopathy is precipitated in a situation where the converse, chronic plumbism, might be expected. This effect of sunlight explains in part why the majority of patients with lead poisoning are seen on the pediatric wards during the summer months.

A solution to the first dilemma, absence of diagnostic tools, came almost as a deluge around 1930 when three American workers, John Caffey,[3] E. A. Park,[4] and E. C. Vogt[5]

[1] Ruddock, J. C. *J.A.M.A.*, 1924, *82*, 1682.

[2] Rapaport, M., and Rubin, M. I. *Am. J. Dis. Child.*, 1941, *61*, 245.

[3] Caffey, John. *Radiology*, 1931, *17*, 1957.

[4] Park, E. A. *Am. J. Dis. Child.*, 1930, *39*, 905.

[5] Vogt, E. C. AM. J. ROENTGENOL. & RAD. THERAPY, 1930, *24*, 550.

demonstrated almost simultaneously that a recognizable metallic band appeared at the ends of growing bones in infants and small children absorbing appreciable amounts of lead. In 1933 Doctor Park[6] summarized the characteristics of the radiopaque lead line with a completeness which requires no essential additions today.

Probably no other single observation in modern pediatrics affected the study of a disease more profoundly than did the discovery of the lead line in plumbism. It brought to an end the "Case Report" era and as large series of well analyzed data became available the entire natural history of lead poisoning was rewritten. It was soon realized that while occasional local or sporadic events might distort temporarily the image, poisoning in childhood was due to the ingestion of paint which could be gnawed from toys, furniture, and surfaces or consumed as flakes after time and weather had led to separation from walls and woodwork. Pica became standard consideration in the student's amanuensis while, more important, cooperative steps were taken immediately to eliminate the use of lead pigment and base from articles likely to be available for chewing.

The frequency with which death occurred during the acute phase of poisoning was now appreciated as was the observation that demise could usually be ascribed to the terrific intracranial pressure which characterized the meningoencephalopathy. The roentgenologist was able to exhibit films in which suture lines were literally torn apart and this led logically to advocacy of bilateral temporal decompression as an emergency measure;[7] a technique not infrequently used on our service today. Study of a large group of children who had "recovered" from lead poisoning brought Byers and Lord[8] to point out not only the frequency of overt residual damage to the nervous system but to emphasize how many of these survivors revealed personality difficulties and alterations in behavioral development; a phase in the story which needs reappraisal today under condiditions of present therapy.

Increasing early recognition of cases led to better studies of the metabolic and biochemical aspects of plumbism. One outcome of these has been further observations on porphyrinuria and the current effort to develop a rapid, inexpensive, and simple screening test based on this phenomenon.[9] Quantitative determinations of coproporphyrin in the urine are also being employed tentatively as an estimate of continuing lead effect.

A final phase in the story might be the observation that Ruddock's lead world has been shrinking until now it is almost a microcosm composed of neglected surfaces from which paint is crumbling and peeling. Modern methods and styles in decorating and building have relegated the main threat to the older and more poorly maintained portions of our communities. Current lead poisoning thus becomes a problem largely of health departments and belongs in the same position as unsafe fire escapes, outdoor privies, and rodent control.

The evolution of therapy can be traced to the fundamental concepts developed by Aub's group during the 1920's;[10] that lead parallels calcium in much of its behavior, that by far the greatest amount of lead in the body is deposited in bone as a relatively inert salt, and that the symptoms of poisoning arise from the fraction which either circulates within the blood or is contained by viscera and other soft tissues. Obviously, on these premises, two directions for therapy can be defended; measures can be taken to increase the amount of lead deposited as inert phosphate or efforts can be made to bind the active fraction and encourage its excretion. Space does not permit review of the early efforts endorsed for the accomplishment of either aim; the use of vitamin D, modifications in ratios of calcium and

[6] Park, E. A., *et al. J. Pediat.*, 1933, *3*, 265.
[7] Ingraham, F. D. *Surg., Gynec. & Obst.*, 1938, *67*, 811.
[8] Byers, R. K., and Lord, E. E. *Am. J. Dis. Child.*, 1943, *66*, 471.
[9] Chisolm, J. J., and Harrison, H. E. *Pediatrics*, 1956, *18*, 943.
[10] Aub, J. C., *et al. Medicine*, 1925, *4*, 1.

phosphorus, electrolysis, and citrate treatment.

Since the second World War, two compounds have seemed to approximate the theoretically ideal antidote and each is in present use. The first, British Anti Lewisite (BAL) was developed primarily as a decontaminant for arsenic and accomplished this purpose through the binding of the element, in competition with cell surface groups, by virtue of two active sulfhydryl radicles. When adapted to the treatment of lead poisoning experiences varied. We here were quite impressed by the fact that the compound formed was innocuous, that it was easily eliminated in the urine and that the final result was marked decrease in the total amount of active lead. The second substance was introduced more recently and has found greater favor with most workers. Ca EDTA (disodium, calcium, ethylene diamine tetra acetic acid) belongs in the group of substances known as chelates or claw compounds. They are capable of binding a variety of metals in accordance with relative dissociation constants. The product formed in the case of lead is surprisingly stable and inert yet quite easily excreted in the urine. At the moment the substance is administered parenterally in either constant or intermittent doses for periods of five to seven days. During this time clinical improvement is rapid, porphyrin excretion decreases, and red blood cell destruction ends.

Modifications of this program, no doubt, will be numerous and varied for a number of questions are unanswered. Obviously much lead remains after an initial period of therapy since only some twenty milligrams are excreted. But the daily moiety declines toward the end of the period and since little is known of the toxicity of EDTA over extended periods of use an arbitrary termination must be set. Retreatment then becomes a problem, as equilibrium within the tissues is re-established. A second course given after two weeks rest again results in increased urinary loss of a degree less than that during the initial period. If analogy with BAL can be extended to EDTA, then repetitions of treatment over periods of months will cause increased excretion but at a constantly diminishing level. The question, of course, remains, what is a safe level of lead in blood and tissues? Chisolm[11] has answered this at the moment by using quantitative determinations of coproporphyrin as a guide to the continuing physiologic effect of lead and we, during the BAL era, found reticulocyte counts to be a rough indicator. Corollary questions obviously might be, what is the relation of these guides to the danger of continuing brain injury, and what is the risk of deleterious effects in the event of subsequent mobilization of skeletal lead, such as might occur during infection or diarrhea, so long as a large bone depot remains? Experience undoubtedly will provide answers and, in the meantime, it is reassuring to have as satisfactory an agent available as we do.

Besides this basic philosophy of therapy several incidental points should be mentioned. We have already touched on the danger inherent to intracranial pressure during the acute phase and this frequently demands delicate management of fluid intake and output. Again, we have not hesitated to intervene surgically when survival is at stake. Several workers have pointed out that since EDTA increases solubility of lead, it is undesirable to begin therapy so long as flakes of paint remain in the abdomen—a state easily determined by a simple roentgenogram. Finally, all therapy is wasted if a child is sent back into the environment where trouble originally started. Thus, the period of hospitalization should be utilized for thorough inspection of the house and removal of sources for new contamination. The public health and oriented physician will also not miss this opportunity to look for other cases in the same milieu.

Paul V. Woolley, Jr., M.D.

Children's Hospital of Michigan
5224 St. Antoine
Detroit, Michigan

[11] Chisolm, J. J., and Harrison, H. E. *Pediatrics*, 1957, *19*, 2.

SOCIETY PROCEEDINGS* AND NEWS ITEMS

NINTH INTERNATIONAL CONGRESS OF RADIOLOGY

The Ninth International Congress of Radiology will be held from July 23 to 30, 1959 in Munich, Germany. Prof. Dr. Boris Rajewsky of Frankfurt am Main, Germany has been elected President by the International Committee. Prof. Dr. Hans V. Braunbehrens of Munich, Germany has been elected General-Secretary. Dr. Victor Loeck as Executive Secretary is in charge of the Secretarial Office of the Congress.

All information on the congress may be obtained from the Secretarial Office of the Congress, Forsthausstrasse 76, Frankfurt am Main, Germany.

DR. ROBERT R. NEWELL HONORED

Radiologists and other colleagues from many parts of California, including many of his former residents and students, gathered in San Francisco on June 17 at a testimonial dinner honoring Dr. Robert Reid Newell on the occasion of his retirement as Professor of Medicine and Biophysics at Stanford University School of Medicine. A Festschrift issue of the *Stanford Medical Bulletin*, containing contributed papers of general interest in the fields of radiology, radiobiology, and biophysics, is being prepared in his honor for release in August, 1957.

Dr. Newell received the M.D. degree at the University of California in 1916. He served successively as Instructor, Assistant Professor, Associate Professor, and Professor and head of the Department of Radiology at Stanford University School of Medicine from 1920 through 1947. In 1947 he resigned to take a sabbatical leave and devote himself to the new field involving the clinical use of radioactive isotopes. He returned in 1948 as Professor of Biophysics in the Department of Medicine, where he established an active isotope laboratory.

Dr. Newell has had a distinguished career of service in radiology and radiologic physics, where his particular interests and orientation have been of inestimable value in his service on the International Committee on Radiation Protection, Committee on Radiologic Units, Standards and Protection of the American College of Radiology, etc. He is past President (1951) and Fellow of the American College of Radiology, a Fellow of the American Medical Association, and a member of the Radiological Society of North America (Carman Lecturer in 1946), American Roentgen Ray Society, Optical Society, Association of Physics Teachers, Pacific Roentgen Society, San Francisco Radiological Society, California Academy of Medicine (President, 1939), and the Commonwealth Club of California.

The Stanford University Medical Staff announces a testimonial dinner honoring Dr. Robert R. Newell on his retirement from Stanford and his new appointment as consulting scientist, Naval Radiological Defense Laboratory, Hunter Point, San Francisco. This will be held at the Fairmont Hotel, San Francisco, on Monday, September 30, 1957. For reservations, contact Dr. J. Ward Smith, Office of the Dean, 2398 Sacramento Street, San Francisco 15, California, prior to September 15, if possible.

BLOCKLEY RADIOLOGICAL SOCIETY HONORS JAMES WEATHERWAX

On May 11, 1957, the Third Annual Dinner of the Blockley Radiological Society was held in the Barclay Hotel in Philadelphia. This Society consists of the present residents and all of the ex-residents in Radiology at the Philadelphia General

* The list of Meetings of Radiological Societies appears in the July, 1957, issue of the JOURNAL, and will be published in the November number.

Hospital. The purpose of the organization is to honor the chiefs of the X-ray Department, namely Drs. Bernard P. Widmann, Herman Ostrum and Russell Miller.

At this meeting, Mr. James Weatherwax was made an Honorary Member of this Society. Mr. Weatherwax was the founder of the Physics Department of the Philadelphia General Hospital. He was given a scroll which read as follows:

"This scroll is presented to James L. Weatherwax, pioneer physicist, distinguished teacher, author, scientist, scholar and founder of the Physics Department of the Philadelphia General Hospital, by the Blockley Radiological Society. In appreciation of the above achievements, he has been elected an Honorary Member."

We regret to announce the death on July 28, 1957, of Dr. Ira H. Lockwood, a distinguished member of the American Roentgen Ray Society and the American Radium Society.

BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

Radiology of the Alimentary Tract in Infancy. By Roy Astley, M.B., M.R.C.S., D.M.R., Radiologist, The Children's Hospital, Birmingham; Clinical Lecturer in Radiology and Lecturer in Radiological Anatomy, University of Birmingham, England. Cloth. Price, $10.00. Pp. 287, with numerous illustrations. Edward Arnold (Publishers) Ltd., London. In United States: The Williams & Wilkins Co., Mount Royal and Guilford Avenues, Baltimore 2, Maryland, 1956.

This book presents a compact, readable, and authoritative treatise on radiological aspects of pediatric gastroenterology. It deals primarily with the examination of the infant during the first year of life, a subject seldom fully explored in more general radiology texts.

Dr. Astley draws from a broad personal experience, but the latest American and British literature is freely quoted. The subject material is divided into sections on the esophagus, diaphragm, stomach, small intestine and peritoneum, colon, and a miscellaneous group comprising other intraperitoneal and retroperitoneal structures. It is most gratifying to find the book so excellently illustrated with more than two hundred superb negative roentgenograms. Diagrams and tables are advantageously employed. The text is documented by a considerable number of brief case histories well chosen to emphasize the author's conclusions. In the interest of brevity, no formal description of the normal infant was attempted.

Pediatric radiology presents problems in diagnosis and technical procedures much different from those encountered in adult practice. This text will be of immeasurable aid in surmounting these problems for not only the experienced and fledgling radiologists but for the pediatrician and pediatric surgeon as well.

Arch H. Hall, M.D.

Le Traitement des Angiomes Chez les Enfants. By Simone Laborde, Chef de Service Honoraire de l'Institut G. Roussy. Paper. Price, 1,850 fr. Pp. 174, with 71 illustrations. Masson et Cie, Éditeurs, 120 boulevard Saint-Germain, Paris 6e, France, 1956.

This monograph is based on the observations of 2,344 hemangiomas. Port-wine spots may yield easily to electrocoagulation. Thin tuberous cutaneous hemangiomas may be treated with cryotherapy, with or without sclerosing injections, Curie therapy or contact therapy. Larger cutaneous and subcutaneous hemangiomas are better treated with roentgen therapy and especially Curie therapy. In selected cases surgical exeresis may be of value as a primary procedure or following irradiation.

Radiation therapy may produce unwarranted side effects if bad technique is used, especially if the dose is too large. Acute radiodermatitis may result in necrosis and secondary infection of the skin. Chronic radiodermatitis may result in atrophy or telangiectasis and may even give rise to cutaneous cancer. Regions in which there is growing bone or cartilage should be treated very carefully or future growth is affected. While adult muscle is quite radioresistant, in infants doses large enough to effect bone changes may also result in atrophy of muscle. The mammary gland of infants is quite susceptible to damage by excessive irradiation. Great care should be exercised to protect the eyes and central nervous system in treating infants.

Hemangiomas treated during a period of growth are more radiosensitive than those which have attained a stable phase of evolution. In general, it is advisable to be patient, and to undertreat rather than overtreat lesions. Beta emitters such as radiophosphorus and strontium applicators are used only for thin lesions. Thicker lesions may be implanted with low-intensity radium or cobalt needles.

The hemangioma may continue to recede for two or three months after the original treatment, so if additional treatment is needed a waiting period of three to six months is desirable.

Photographs of specific cases are shown before and after treatment, with details of therapy given for each patient.

This comprehensive monograph constitutes a valuable addition to our knowledge concerning what may be at times very troublesome lesions.

Charles M. Nice, Jr., M.D., Ph.D.

Das Skelett des Kindes; Entwicklung, Bildungsfehler und Erkrankungen. Von Doz. Dr. W. Swoboda, Wien. Cloth. Price, DM 48.—. Pp. 184, with 199 illustrations. Georg Thieme, Herdweg 63, Stuttgart, Germany, 1956.

This monograph, devoted to the roentgenology of bones in childhood, begins with a description of the "normal" growing skeleton. Systemic and localized developmental disturbances are presented in separate chapters. The section on endocrine bone changes contains a table which lists the causes and characteristics of dwarfism. Adequate space is given to the osseous manifestations of nutritional and metabolic disturbances. Bone alterations of inflammatory and toxic origin and those caused by diseases of the lympho-reticulo-endothelial system are also well covered, but only selected conditions are discussed in the chapters on bone tumors and on traumatology. Although the bibliography does not neglect the classics in this field, preference has been given to recent publications.

The omissions (for instance, non-osteogenic fibroma, localized gigantism, hemophilia, oxalosis, Addison's disease) are few, far apart, and of limited significance. While it is understandable that an extensive discussion of fractures and dislocations may have been out of order, one would certainly welcome a more detailed presentation of neoplasms. Furthermore, not everybody will agree with the places allocated to the various entities; for instance, the bone lesions in reticulosarcoma, leukemia, and Hodgkin's disease are not described together with bone tumors, but rather are listed right after collagen diseases, in the chapter devoted to lympho-reticulo-endothelial conditions. Still, these are only minor faults, and most of the chapters are excellent.

This text will be a valuable addition to the library of any radiologist. The elegant format, a trademark with this publisher, is an added incentive to acquire the book.

E. R. N. Grigg, M.D.

BOOKS RECEIVED

La Pneumopelvigrafia nella Diagnosi dei Tumori Ginecologici. By G. Carnevali, U. Lucarelli, and P. Paracchi. Cloth. Pp. 196, with 64 illustrations. Casa Editrice Renzo Cortina, Pavia, Italy, 1957.

Leukaemia and Aplastic Anaemia in Patients Irradiated for Ankylosing Spondylitis. By W. M. Court-Brown, O.B.E., M.B., B.Ss., F.F.R., and R. Doll, O.B.E., M.D., F.R.C.P. Paper. Price, $1.89. Pp. 135, with figures and tables. The Medical Research Council and Her Majesty's Stationery Office, London, 1957. Available through: British Information Services, 30 Rockefeller Plaza, New York 20, New York.

Magnetic Removal of Foreign Bodies. By Murdock Equen, M.D., F.A.C.S., Founder and Chief of Staff of Ponce de Leon Infirmary, Atlanta, Georgia. Cloth. Price, $4.50. Pp. 94, with 116 illustrations. Charles C Thomas, 301 East Lawrence Avenue, Springfield, Illinois, 1957.

Topographische Ausdeutung der Bronchien im Röntgenbild. By Priv.-Doz. Dr. C. Esser, Mainz. Second edition. Cloth. Price, DM 58.—. Pp. 210, with 89 illustrations. Georg Thieme, Herdweg 63, Stuttgart, Germany, 1957.

Bronchopulmonary Diseases; Basic Aspects, Diagnosis and Treatment. Edited by Emil A. Naclerio, M.D., Chief of the Thoracic Surgical Services, Harlem and Columbus Hospitals, New York. Cloth. Price, $24.00. Pp. 956, with 719 illustrations. Paul B. Hoeber, Inc., 49 East 33rd Street, New York 16, New York, 1957.

Tumors of the Pituitary Gland and Infundibulum. Atlas of Tumor Pathology. Section X—Fascicle 36. By James W. Kernohan, M.D., Chairman, Sections of Pathologic Anatomy and Surgical Pathology, Mayo Clinic, Rochester, Minnesota, and Professor of Pathology, Graduate School, University of Minnesota, Minneapolis, Minnesota; and George P. Sayre, M.D., Section of Pathologic Anatomy, Mayo Clinic, Rochester, Minnesota, and Assistant Professor of Pathology, Graduate School, University of Minnesota, Minneapolis, Minnesota. Paper. Price, $1.00. Pp. 81, with 67 illustrations. Published by the Armed Forces Institute of Pathology under the Auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Washington, D. C., 1956. For sale by the American Registry of Pathology, Armed Forces Institute of Pathology, Washington 25, D. C.

Tumors of the Kidney, Renal Pelvis and Ureter. Atlas of Tumor Pathology. Section VIII—Fascicle 30. By Balduin Lucké, M.D., Dr. P.H., Late Professor of Pathology, University of Pennsylvania, Philadelphia; and Hans G. Schlumberger, M.D., Professor of Pathology, Ohio State University, Columbus, Ohio. Paper. Price, $2.25. Pp. 208, with 187 illustrations. Published by the Armed Forces Institute of Pathology under the Auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Washington, D. C., 1957. For sale by the American Registry of Pathology, Armed Forces Institute of Pathology, Washington 25, D. C.

TUMORS OF THE EYE AND ADNEXA. ATLAS OF TUMOR PATHOLOGY. Section X—Fascicle 38. By Algernon B. Reese, M.D., Attending Surgeon and Pathologist, Institute of Ophthalmology, New York City; Clinical Professor of Ophthalmology, College of Physicians and Surgeons, Columbia University; Ophthalmologist to Memorial Center for the Treatment of Cancer and Allied Diseases, New York City. Paper. Price, $2.00. Pp. 205, with 122 illustrations. Published by the Armed Forces Institute of Pathology under the Auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Washington, D. C., 1957. For sale by the American Registry of Pathology, Armed Forces Institute of Pathology. Washington 25, D. C.

ABSTRACTS OF RADIOLOGICAL LITERATURE

Department Editor: T. Leucutia, M.D., Harper Hospital, Detroit 1, Michigan

INDEX TO ABSTRACTS

ROENTGEN DIAGNOSIS

Neck and Chest

Zuppinger, A., and Frank, L.: Recent contributions to the roentgenologic examination of the thorax 556

Nelson, S. W.: Large pneumothorax and associated massive collapse of the homolateral lung due to intrabronchial obstruction; a case report 556

Weissman, I., Worden, J. P., and Christie, J. M.: Mediastinal parathyroid carcinoma with metastases; report of a case and review of the literature 556

Grosse-Brockhoff, F., Koch, D., Loogen, F., Rotthoff, G., Vieten, H., and Willmann, K. H.: The use of carbon dioxide as contrast medium for visualization of the heart and great vessels 556

Höffken, W., Junghans, R., and Zylka, W.: The bases of pneumoradiography of the right heart with carbon dioxide 557

Hansbrough, E. T., and Lipin, R. J.: Intrathoracic accessory lobe of the liver 557

Rosenblum, D., Nussbaum, A., and Schwartz, S.: Partial obstruction of the inferior vena cava by herniation of the liver through the foramen of Morgagni; a case report 557

Abdomen

Yarnis, H., Marshak, R. H., and Crohn, B. B.: Ileocolitis 558

Snow, W., and Hollingsworth, J. C.: Self-retaining barium-enema tip: Improvement. 558

Gynecology and Obstetrics

Posner, A. C., and Goldman, J. A.: A case of osteogenesis imperfecta congenita diagnosed in utero 558

Engle, R. B., Jacobson, G., and Fraser, E. R.: Soft-tissue placentography in diagnosis of bicornuate uterus 559

Genitourinary System

Zeitel, B. E., Lentino, W., Jacobson, H. G., and Poppel, M. H.: Renografin: A new intravenous urographic medium 559

Arendt, J., and Zgoda, A. The heterotropic excretion of intravenously injected contrast media 560

Walter, R. C., and Goodwin, W. E.: Aortography and pneumography in children 560

Strittmatter, W. C., Brown, C. H., and Tretbar, H. A.: A large carcinoma of the adrenal; report of a case 560

Lefkovits, A. M.: Fatal air embolism during presacral insufflation of air 561

Lich, R., Jr.: The obstructed ureteropelvic junction 561

Loitman, B. S., and Chiat, H.: Ureteritis cystica and pyelitis cystica; a review of cases and roentgenologic criteria 561

Skeletal System

de Reus, H. D. Bone infarct 562

Grainger, R. G., and Laws, J. W. Paget's disease—active or quiescent? 562

Bream, C. A., and Sprunt, W. H., III.: An unusual cystic lesion of bone, limited to the pelvis and lower extremities; osteogenesis imperfecta cystica? 563

O'Connor, S. J., and Ivanoff, J. C.: Infantile cortical hyperostosis 563

Meany, T. F., and Hays, R. A.: Roentgen manifestations of psoriatic arthritis 563

Gibson, H. J.: Ankylosing spondylitis: Aetiology and pathology 563

Stoll, B. A.: Ankylosing spondylitis: Its hormonal background in relation to x-ray therapy 564

Blood and Lymph System

Poser, C. M., and Taveras, J. M.: Cerebral angiography in encephalo-trigeminal angiomatosis 565

Schmidt, J.: Roentgen diagnostic features of the arteria lusoria 565

Steiner, R. E., Sherlock, S., and Turner, M. D.: Percutaneous splenic portal venography 565

ROENTGEN DIAGNOSIS

NECK AND CHEST

ZUPPINGER, A., and FRANK L. Neueres zur Thorax-Röntgenuntersuchung. (Recent contributions to the roentgenologic examination of the thorax.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, April, 1957, *86*, 419–431. (From: Röntgeninstitut der Universität und des Inselspitals, Bern, Switzerland.)

A modified combination table is described which facilitates changes from the erect to the horizontal position and from anteroposterior to lateral position with a minimum of time and inconvenience. The roentgenographic tube can also be quickly changed from the vertical to the horizontal beam direction. With the routine use of the table, in borderline cases, occult pleural effusions and obscure chest lesions have been discovered with ever increasing frequency.

Emphasis is laid on the horizontal roentgen beam, with the patient lying on either side, for recognition of shifting pleural effusions. This study has also proved valuable for excluding pleural thickening and adhesions, for confirmation of encapsulation and for atypically located effusions. The method has been helpful in pulmonary lesions with associated pleural effusion, in atelectasis with simultaneous pleural adhesions, in eventration of the diaphragm, in the differentiation of pleural effusion and thickening, and in mediastinal shift and displacement.

The authors have also used the special table for bronchography, for studying the influence of the lateral position on heart movements, for pendulum movements of the mediastinum with gravity changes of the thorax, and for position and movement of the diaphragm when the patient lies on the left or right side.

For discovery of small effusions, best results are achieved when the roentgen ray exposure is made in expiration with the patient lying on the affected side.

Numerous roentgenographic reproductions illustrate the accomplishments with the method. A special table, as described and illustrated, tends to encourage the utilization of an important view which has been described many years ago, but has apparently not become sufficiently popular as yet.—*Ernest Kraft, M.D.*

NELSON, SIDNEY W. Large pneumothorax and associated massive collapse of the homolateral lung due to intrabronchial obstruction; a case report. *Radiology*, March, 1957, *68*, 411–414. (Address: Department of Radiology, Ohio State University, Columbus 10, Ohio.)

A case of massive pulmonary collapse (atelectasis) with homolateral pneumothorax is presented. The complication occurred suddenly four days after subtotal gastrectomy, evidenced by dyspnea and orthopnea. A chest roentgenogram showed a right pneumothorax with collapse of the right lung, which was displaced, with the mediastinum, toward the side of the pneumothorax. There was moderate elevation of the right hemidiaphragm. The diagnosis on the basis of these findings was "large negative-pressure right pneumothorax with associated complete atelectasis of the right lung due to intrabronchial obstruction." Removal of thick tenacious mucoid material from the right main stem bronchus, institution of closed chest drainage, and subsequent tracheotomy to facilitate removal of secretions, resulted in rapid and continuous improvement.

Each of these 2 conditions is, in itself, an acute medical emergency requiring immediate treatment. Early diagnosis may prevent serious sequelae, since the 2 conditions can be treated concomitantly.—*A. W. Sommer, M.D.*

WEISSMAN, IRVING, WORDEN, JAMES P., and CHRISTIE, JAMES M. Mediastinal parathyroid carcinoma with metastases; report of a case and review of the literature. *Radiology*, March, 1957, *68*, 352–357. (Address: I. Weissman, Christie Clinic, Champaign, Ill.)

The authors present a case report of a mediastinal parathyroid adenoma with distant metastases, eventually leading to death. On postmortem examination the masses in the mediastinum, in addition to multiple metastatic areas, proved to be parathyroid carcinoma. Six years previously, a large lobulated mass, measuring 15.5×18 cm., had been removed from the mediastinal region of this patient. The pathologic conclusions at this time showed a difference of opinion. It was diagnosed "ectopic parathyroid adenoma," although the local pathologist considered the tumor to be an adenocarcinoma. The case is unusual in that, in spite of the large size of both the benign and malignant parathyroid tumor, no evidence of osteitis fibrosa cystica occurred. The diagnosis was confirmed by the abnormal calcium and phosphorus levels in the blood, and at necropsy.

Primary carcinoma of the parathyroid gland is rare, and the exact histologic criteria necessary for such a diagnosis are equivocal. In most of the recorded cases, the evidence of malignancy lies in the tendency of the tumor to recur locally, with return of symptoms of parathyroid intoxications. Typical cystic changes in the bones are not always found in parathyroid carcinoma.—*A. W. Sommer, M.D.*

GROSSE-BROCKHOFF, F., KOCH, D., LOOGEN, F., ROTTHOFF, G., VIETEN, H., and WILLMANN, K. H. Kohlendioxyd als Kontrastmittel für die Röntgendarstellung des Herzens und der Gefässe. (The use of carbon

dioxide as contrast medium for visualization of the heart and great vessels.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin.*, March, 1957, *86*, 285–291. (From: Medizinische Klinik und Röntgeninstitut der Chirurgischen Klinik der Medizinischen Akademie, Düsseldorf, Germany.)

Following the experiments of Durant, Oppenheimer, Stauffer and associates, with intravenous injections of carbon dioxide for angiocardiography, the authors of this article were able to confirm in experiments with dogs, the diagnostic value and absence of harmful effects of this procedure.

Two patients were examined by this method, both with hypersensitivity to iodine containing contrast substances. In the first patient, 150 cc. of carbon dioxide was injected through a catheter into the right ventricle and an isolated stenosis of the pulmonary artery was demonstrated roentgenographically. The second patient was also successfully examined by this method and a pulmonary stenosis was visualized.

Femoral arteriograms, with up to 200 cc. of carbon dioxide, were painless and without harmful effects. Experiments with thoracic and abdominal aortography are in progress; here it is important to avoid the entry of greater quantities of carbon dioxide into the coronary and cerebral vessels to prevent myocardial and cerebral damage.

The article contains 7 roentgenographic reproductions and numerous references.—*Karol E. Matzinger, M.D.*

Höffken, W., Junghans, R., and Zylka, W. Die Grundlagen der Pneumoradiographie des rechten Herzens mit Kohlendioxyd. (The bases of pneumoradiography of the right heart with carbon dioxide.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, March, 1957, *86*, 292–301. (From: Röntgenabteilung des Bürgerhospitals in Köln, und der Medizinischen Universitäts-Poliklinik Köln, Bürgerhospital, Köln, Germany.)

Intravenous injection of carbon dioxide in experimental animals (white rats, rabbits and dogs) produced tachycardia lasting in the average, eighteen seconds and followed by normal pulse rate. The blood pressure showed a rapid decrease lasting twenty to thirty seconds. Tachypnea lasting an average of ninty seconds and increased respiratory minute volume were also noted. Large sublethal doses produced apnea and sudden collapse about ten seconds after injection, with recovery. Lethal doses produced collapse with apnea, convulsions and death.

Serial roentgenograms showed filling of the vena cava superior, the right ventricle and pulmonary artery and gradual absorption of the gas. The whole process lasted ten to twenty seconds. On comparing the lethal doses for various experimental animals, the authors found a fairly constant relationship between the lethal dose of carbon dioxide in cubic centimeters and the heart minute volume, which in dogs was 1.10, in rabbits 1.8. Assuming a similar relationship for man, the lethal dose for an adult with a minute volume of 4,000 cc. would be 400 cc. of carbon dioxide.

The cause of death in animals was blocking of the right heart and pulmonary circulation by carbon dioxide with cerebral ischemia.

The method is of value in visualization of the vena cava superior, the right auricle, tricuspid valve, right ventricle and pulmonary artery. The dose injected in humans was 100 to 150 cc., which caused no complications.—*Karol E. Matzinger, M.D.*

Hansbrough, Eugene T., and Lipin, Raymond J. Intrathoracic accessory lobe of the liver. *Ann. Surg.*, April, 1957, *145*, 564–567. (From: The Surgical Service, Veterans Administration Hospital, Little Rock, Ark.)

A case of abnormal lobe of liver in the right chest is reported. Pneumoperitoneum revealed a mass above the right diaphragm. Preoperatively it was thought to be a tumor, either benign or malignant. The other possibilities considered, were a collection of fluid in the pleural space, localized cyst and an inflammatory lesion.

The accessory hepatic lobe had a pedicle which contained an artery, vein and liver duct which was invested by the diaphragmatic pleura, musculature and peritoneum. The pedicle entered the hepatic substance immediately after perforating the diaphragm. The removed mass weighed 137 grams. Microscopically, the accessory lobe showed evidence of cirrhosis.—*C. Peter Truog, M.D.*

Rosenblum, David, Nussbaum, Arnold, and Schwartz, Solomon. Partial obstruction of the inferior vena cava by herniation of the liver through the foramen of Morgagni; a case report. *Radiology*, March, 1957, *68*, 399–402. (Address: D. Rosenblum, Jewish Hospital of Brooklyn, Brooklyn 38, N. Y.)

The authors report a case of herniation of the liver through the foramen of Morgagni, with partial obstruction of the inferior vena cava. The patient, a three year old white boy, was admitted for evaluation of a mass in the right cardiophrenic angle. Diagnostic pneumoperitoneum revealed liver herniation through the anteromedial portion of the diaphragm. Angiocardiography showed a sharp kink in the inferior vena cava just beneath the diaphragm. Preferential blood flow occurred through the paravertebral plexus, azygos system and transhepatic collaterals. At operation, the preoperative diagnosis of liver her-

niation and kinking of the vena cava was confirmed. Convalescence was uneventful.

Herniation through the foramen of Morgagni constitutes approximately 2.5 per cent of all congenital diaphragmatic hernias. The presence of liver in this type of hernia has been reported with relative frequency prior to the age of twelve. Its rarity beyond this age indicates its relationship to longevity. Whether or not obstruction of the inferior vena cava may play a role is not known.—*Arno W. Sommer, M.D.*

ABDOMEN

YARNIS, HARRY, MARSHAK, RICHARD H., and CROHN, BURRILL B. Ileocolitis. *J.A.M.A.*, May 4, 1957, *164*, 7–13. (Address: H. Yarnis, 1075 Park Ave., New York, N. Y.)

The granulomatous nature of regional ileitis and the exudative inflammatory process of the typical case of ulcerative colitis is well recognized and undisputed. Warren and Sommers regard the two diseases as morphologically different and deny the existence of granulomatous colitis. Neuman and Dockerty reported 25 resected specimens of segmental colitis in which there was a nonspecific granulomatous process producing thickening of the entire colonic wall.

The authors feel that regional ileitis may be associated with ulcerative colitis or granulomatous colitis. They use the term "combined ileocolitis" to signify the presence of granulomatous ileitis and ulcerative colitis. When granulomatous ileitis is combined with granulomatous colitis, the term "granulomatous ileocolitis" is used. If the combination of the two diseases occurs simultaneously, it is called synchronous or if it occurs in sequence it is called metachronous.

The authors report 60 cases of ileocolitis and only 2 of these cases were granulomatous ileocolitis. In 40 cases both ileitis and ulcerative colitis were present at onset of the disease and the combined ileocolitis was therefore "synchronous" in origin. In 18 cases either ulcerative colitis or ileitis was originally present, but after an attempt to cure the original disease by surgical intervention, the second disease developed. This group of combined ileocolitis was called "metachronous" in nature indicating that the combined diseases succeeded or followed each other.

It is important roentgenographically to differentiate regional ileitis from the so-called "backwash" ileitis, which may be associated with diffuse ulcerative colitis or right sided segmental colitis. The authors find that in backwash ileitis, the narrowing of the intestinal lumen was not as marked as when there was granulomatous involvement. The mucosa usually presented minimal ulceration; fistula formation was rare; skip areas were not seen; and marked separation of the intestinal loops was not usually observed. However, some of these cases showed marked ulceration of the mucosa as well as considerable spasm with a "string sign."

The granulomatous nature of the lesion in the ileum could be identified fairly accurately, but this was not so in lesions involving the colon. It was assumed that in cases where a typical ileitis was associated with involvement of a short segment of the colon in continuity, the colon lesion was also granulomatous in origin.

The clinical aspects of ileocolitis are considered.

Medical treatment should be attempted in all cases of ileocolitis, unless there are definite indications for surgery. Details of medical therapy and of surgical management are discussed.—*C. Peter Truog, M.D.*

SNOW, WILLIAM, and HOLLINGSWORTH, JOHN C. Self-retaining barium-enema tip: Improvement. *Radiology*, March, 1957, *68*, 418. (Address: W. Snow, VA Center, Shreveport, La.)

The authors describe the use of a stiff metal wire, of a number 8 gauge, inserted into the self-retaining balloon-type enema tip to make possible the introduction of the tip without loss of time or use of gloves. The wire is inserted to within an inch of the rubber tip so that injury to the anus or rectum is avoided. Following placement of the enema tip the wire is removed and the barium enema procedure is carried on as usual.—*Donald N. Dysart, M.D.*

GYNECOLOGY AND OBSTETRICS

POSNER, A. CHARLES, and GOLDMAN, JACK A. A case of osteogenesis imperfecta congenita diagnosed in utero. *Am. J. Obst. & Gynec.*, May, 1957, *73*, 1143–1147. (From: Obstetrical Service of the Bronx Hospital, New York, N. Y.)

Osteogenesis imperfecta is a rare disorder characterized by marked fragility of the bones resulting in multiple fractures. The syndrome is hereditary, and the congenital form is usually transmitted as a recessive mendelian trait, while the late form is dominant. It is known that this disorder is a congenital osteoporosis, but unlike other conditions characterized by abnormal fragility of the bones, its etiology has not been discovered.

In osteogenesis imperfecta, there is a marked, generalized osteoporosis of the bones, of both cartilaginous and membranous origin, due to failure of periosteal apposition of bone and defective endosteal bone production. The bones are brittle and exhibit a very thin cortex. The trabeculae are reduced in number and in size and contain less calcium than normal. While the diaphysis of the long bones is deficient and slender, the growth and differentiation of the epiphysis remain normal, which accounts for the contrasting and swollen appearance of these bones. The diameter of the bones may be normal or increased. Fractures, which are common occurrences, heal quickly, and callus formation and absorption are normally rapid and at times even excessive.

The disease takes 2 forms, formerly considered as separate entities, but now proved to be variants of the same condition: (1) The congenital form, osteogenesis imperfecta congenita or fragilitas ossium, is usually more severe than the late form with multiple fractures in the newborn or even in utero. (2) The late form, osteogenesis imperfecta tarda, Lobstein's disease or osteopsathyrosis tarda, is encountered in infants, adolescents, or adults.

Roentgenograms reveal multiple fractures at birth, including old fractures with callus formation and fresh ones due to trauma during and after delivery. Roentgenographic features consist of generalized osteoporosis and diminished density of the bones, as well as hypoplasia and thinning of the cortex with deficient spongiosa. Caffey stated that a pattern of mosaic rarefaction of the bones of the skull is pathognomonic of the disease.

The authors present one case of the disease diagnosed in a routine pelvimetry on a term breech. The mother gave no family history suggestive of bone disease and had normal deliveries of 2 normal children, aged eight and five years.

The roentgenograms showed deformity of the ribs due to multiple healed fractures and a midfemoral shaft fracture with abundant callus. Further studies after a vaginal delivery showed numerous other healed fractures indicating that the disease was well advanced prior to delivery.

The case reported is the first instance of osteogenesis imperfecta congenita in their hospital in a twenty year period, and represents an incidence of 1 in 140,000 deliveries.—*Eugene J. McDonald, M.D*

Engle, Robert B., Jacobson, George, and Fraser, Eleanor R. Soft-tissue placentography in diagnosis of bicornuate uterus. *Radiology*, March, 1957, *68*, 408–410. (Address: R. B. Engle, 1200 N. State St., Los Angeles 33, Calif.)

Anomalies of fusion of the uterus are important as a source of complication during pregnancy. The presentation of a description of the roentgenographic findings which may lead to suspicion of bicornuate uterus is therefore an important contribution to the radiologic literature.

In the 3 cases herein reported, the diagnosis of bicornuate uterus was evident from an anteroposterior soft-tissue placentogram, which showed a modified breech presentation with the head and body toward one side of the abdomen, the sacrum dependent, and the legs separated from the trunk and extending toward the opposite side of the abdomen. This languid posture resembles that assumed by a person lying in a hammock. The separation of the legs from the rest of the body suggests an absence of the usual compressing effect of the uterus, and it may be that the body rests in one uterine horn and the legs in the other. The authors believe that a bicornuate uterus, or one of its variants, may be suspected when the fetus takes this position.

In the differential diagnosis, a transverse lie in a normal uterus must always be considered. This is readily distinguishable, since in this condition the fetal spine shows a greater degree of flexion and the lower extremities are drawn up toward, and frequently are in contact with, the head and upper extremities.—*A. Ralph Watson, M.D.*

Genitourinary System

Zeitel, Bertram E., Lentino, Walter, Jacobson, Harold G., and Poppel, Maxwell H. Renografin: A new intravenous urographic medium. *J. Urol.*, Oct., 1956, *76*, 461–465. (From: Division of Diagnostic Radiology, Montefiore Hospital and Departments of Radiology, Bellevue Hospital and New York University College of Medicine, New York, N. Y.)

In this article the authors present their observations of the roentgenographic quality and allergic reactions associated with the intravenous administration of a new urographic medium in 1,000 unselected consecutive patients.

Renografin contains a mixture of the sodium salt and the methyglucamine salt of triiodobenzoic acid in aqueous solution. It has a specific gravity of 1.4 to 2.0 at 20 degrees centrigrade and a pH of 6.5. Its molecular weight is 613.8 and it contains 62.1 per cent iodine by weight. It is supplied in 20 cc. ampules in a solution of 76 per cent strength. Toxicity studies carried out in laboratory animals with this drug show a wide margin of safety. The drug is rapidly excreted by the kidney after intravenous injection, but the relative role of glomerular filtration and tubular excretion is still unknown.

From the study of 1,000 patients who received this drug for intravenous urography, it was found that 48.8 per cent had superior intensity of opacification and degree of filling of the collecting system of the kidneys; 39.1 per cent had satisfactory intensification and filling and in 12 per cent of the group the degree of opacification or filling was insufficient for diagnosis. The authors conclude that renografin may be considered as an excellent medium for visualization of the collecting-system of the urinary tract.

There were 105 allergic reactions found in 80 patients of the total 1,000 patients who were injected with the new medium. The most common reactions were nausea and vomiting. In 1 patient who had a positive history of asthma, a severe systemic reaction occurred following intravenous injection of 1 cc. of renografin and the examination was therefore discontinued. The most important prognostic evidence of an allergic reaction is the presence of an allergic history. Of 71 patients out of a total of 1,000 who presented a positive allergic history, 57 per cent had

side reactions of an allergic nature. Of 929 patients with no history of allergy only 4 per cent showed side-reactions. The authors observe that skin testing and intra-ocular tests are of no value in the prediction of allergic side-reactions. An intravenous test should be done in all patients who have a history of allergy.—*George. W. Chamberlin, M.D.*

ARENDT, JULIAN, and ZGODA, ADAM. The heterotropic excretion of intravenously injected contrast media. *Radiology*, Feb., 1957, *68*, 238–241. (Address: J. Arendt, Mount Sinai Hospital, California Ave. at 15 St., Chicago 8, Ill.)

An unusual roentgen observation, having only two antecedents in the medical literature, is reported. A contrast medium injected intravenously to demonstrate the kidney was instead taken up by the liver, leading to intense visualization of the gallbladder and the common duct. Possible explanations of this heterotropic excretion include: (1) a pathologic condition of the target organ interfering with proper elimination of the medium and (2) an inundation process due to introduction of too much of the material in too short a time, permitting partial deviation and excretion through an alternative route. Neither of these explanations is fully satisfactory, since neither accounts for the rare occurrence of the reversal and the rapidity of the deflection.

The difference between a pyelographic and cholegraphic medium lies essentially in the nature of the carrier. It is the carrier which controls the pathway, holding the iodine molecule firmly bound and being itself chemically inert. It is to be noted, however, that the concept of an intravenously injected contrast medium as a guided missile, carrying its iodine charge to a selected organ, is correct only if we allow for a large degree of variation and deflection under pathologic conditions. With recognition of the hepatic renal syndrome, neurovascular shunts and hepatotropic reflexes have been found to occur. These vascular shunts may well represent the missing link in the explanation of the 3 cases of heterotropic excretion reviewed in this article.—*A. Ralph Watson, M.D.*

WALTER, ROBERT C., and GOODWIN, WILLARD E. Aortography and pneumography in children. *J. Urol.*, Feb., 1957, *77*, 323–328. (Address: R. C. Walter, 1015 Gayley Ave., Los Angeles 24, Calif.)

Several authors have published objections and reservations regarding the use of translumbar aortography in infants and children. In this article the authors state that, when indicated, the procedure is readily applicable despite early age and small size. They report patients in whom aortography was used 19 times, 17 times by the translumbar technique and 2 times by the percutaneous femoral method. In 3 instances pneumography was combined with aortography. The youngest patient was six weeks of age and the oldest one was twelve years of age. In 7 patients the indication for aortography was the evaluation of congenital anomalies of the upper urinary tract. Six children were studied because of hypertension, 4 were suspected of having an adrenal tumor and 2 were examined for possible vascular disease unrelated to the urinary tract. In every instance the aortograms contributed positive evidence which could be duplicated by no other diagnostic test and which was important in arriving at a final diagnosis.

The authors give their technique in detail and report 2 cases in some detail to illustrate the value and significance of the method.

In this series of patients no serious ill effects were observed from aortography. Two temporary reactions were noted with retroperitoneal pneumography. In 1 case the use of an excessive amount of oxygen in an infant produced distress and a mild shock-like picture for a short time. In another case oxygen diffused into the scrotum producing a balloon-like filling which appeared alarming, but caused no damage.

Certain modifications of techniques in the application of aortography and retroperitoneal pneumography are discussed.—*George W. Chamberlin, M.D.*

STRITTMATTER, W. C., BROWN, C. H., and TRETBAR, H. A. A large carcinoma of the adrenal; report of a case. *Radiology*, Feb., 1957, *68*, 231–233. (Address: W. C. Strittmatter, 2020 East 93rd St., Cleveland 6, Ohio.)

Carcinoma of the adrenal gland is a rare neoplasm and is difficult to diagnose preoperatively. Early diagnosis also is difficult because of the absence of localizing symptoms in the non-hormone-producing growths. This type of tumor usually occurs in persons beyond the age of thirty. Malaise and pain are common presenting symptoms and a mass is often palpable. Lung, lymph node, liver and bone metastases may be evident before the primary tumor can be identified.

Calcification in the adrenal gland is frequently seen secondary to healed tuberculosis and may occur secondary to foreign bodies, hemorrhages, thrombi or dead parasites. Sympathicoblastomas and carcinomas commonly contain calcification, but bone formation in these tumors is extremely rare.

The authors report a case of an adrenal carcinoma which weighed 1,750 gm. and which contained areas of cancellous bone formation. This is the largest such tumor reported in the literature. A preoperative diagnosis of an adrenal tumor had been made following urography and an upper gastrointestinal examination which showed downward displacement of the left kidney and displacement of the stomach by an extrinsic mass respectively. No metastases were found at operation nor have they been demonstrated in the year since surgery.—*Donald N. Dysart, M.D.*

Lefkovits, Aaron M. Fatal air embolism during presacral insufflation of air. *J. Urol.*, Jan., 1957, *77*, 112–115. (From: The General Medicine and Rheumatology Section of the Veterans Administration Medical Teaching Group (Kennedy) Hospital, Memphis 15, Tenn.)

A forty-seven year old male was studied for paroxysmal hypertension. Air in the amount of 1,300 cc. was injected by the usual presacral approach and with the customary precautions. Immediately after moving the patient from the knee-chest position he developed acute hyperpnea, loss of consciousness, cessation of breathing and arrest of pulse. He was placed in the left lateral decubitus position and given artificial respiration, intubation, oxygen and intracardiac epinephrin. He did not respond to these measures and died immediately. At postmortem examination air was found retroperitoneally and in the right auricle and coronary vessels. In addition the coronary vessels showed atheromatous changes and intimal thickening. The adrenal glands were normal.

In the author's series of 14 presacral air injections prior to the fatal case, only mild symptoms of brief duration had been noted. These symptoms were pain over the epigastrium with a choking sensation, dull retrosternal pain, abdominal discomfort, pain in the left upper abdomen, pain in the shoulders on deep inspiration and subcutaneous emphysema. A review of previous literature by 11 other authors revealed 2 fatal cases of air embolism.

Suggestions for precautionary measures to be taken during the performance of this procedure are as follows: (1) strict aseptic conditions, (2) the use of a blunt needle with a sharp obdurator, (3) slow injection of gas, (4) placement of the patient in the left lateral position, (5) constant observation of the patient, (6) availability of a resuscitator and stimulants, (7) auscultation of the heart during the injection of air, (8) readiness to manually massage the heart if necessary.—*George W. Chamberlin, M.D.*

Lich, Robert, Jr. The obstructed ureteropelvic junction. *Radiology*, March, 1957, *68*, 337–344. (Address: 801 Heyburn Building, Louisville 2, Ky.)

The most common site for supravesical congenital obstruction of the urinary tract is the ureteropelvic junction. If a consistently successful corrective surgical procedure for this condition was to be established, the author realized that the first important task was to determine the underlying cause of the obstruction. In the past, the prevalent concept of most physicians was that ureteropelvic obstruction was due to an extrinsic cause, such as an aberrant vessel or a fibrous band. In view of repeated instances in which resection of such an obstructing band or vessel was valueless in relieving ureteropelvic obstruction, it became apparent that the cause of the obstruction must be sought elsewhere. The author therefore carefully studied the intrinsic structure of the abnormal ureteropelvic junction. He found that in most instances of obstructed ureteropelvic junction there appeared valve-like structures that were always directed toward the renal pelvis, acting as an obstruction to the free flow of urine from the pelvis. Normal ureteropelvic junctions were similarly studied and found to be free of valvular areas.

The method of surgical repair of the obstructed ureteropelvic junction is based on the premise that the retention of abnormal tissue in a corrective procedure is basically illogical. The operation consists essentially of the excision of the ureteropelvic junction along with the redundant renal pelvis. A new ureteropelvic junction is created by an anastomosis of the split ureter to the lower portion of the resected renal pelvis and closure of the remaining pelvis. A nephrostomy tube minimizes intrapelvic pressure during healing.

It has been observed that not all instances of repair function with equal efficiency early in the postoperative period. It is the opinion of the author that this may be because the newly formed anastomosis is accomplished in a portion of the ureter where the peristaltic wave is not optimally active. To know precisely at what point to divide the ureter below its junction with the pelvis, may be the key to a more consistent early functional result.—*A. R. Watson, M.D.*

Loitman, Bernard S., and Chiat, Harold. Ureteritis cystica and pyelitis cystica; a review of cases and roentgenologic criteria. *Radiology*, March, 1957, *68*, 345–351. (Address: B. S. Loitman, The New York Hospital, 525 E. 68th St., New York 21, N. Y.)

Ureteritis cystica, pyelitis cystica, and cystitis cystica are similar conditions resulting from chronic inflammation in the urinary tract. According to von Brunn's theory, which is the most widely accepted, cell nests develop from downward proliferation of lining epithelium, separate, and undergo central degeneration to become cysts.

The authors present a series of 57 cases, including 25 cases of pyelo-ureteritis cystica and 32 of cystitis cystica. Evidence of urinary tract infection was found in 52 cases. The diagnosis of pyelitis and ureteritis cystica was made by intravenous pyelography, retrograde pyelography, surgical pathology, or autopsy. Of the 32 cases of cystitis cystica presented, 30 were diagnosed by cystoscopy and the diagnosis confirmed by biopsy in 11 cases. Two cases were found at autopsy.

With pyelograms of good quality, the diagnosis of ureteritis cystica and pyelitis cystica is usually not difficult. Multiple small, round, radiolucent defects, producing a characteristic scalloping of the ureteral margins when viewed in profile, are seen. The cysts are usually scattered and discrete, but may occasion-

ally cluster in small groups. They may be either unilateral or bilateral in distribution. Because of the frequent association with chronic inflammatory disease of the urinary tract, it is not surprising to find roentgenographic changes of both pyelo-ureteritis cystica and chronic pyelonephritis occurring concomitantly.

A number of conditions must be considered in the roentgenographic differential diagnosis of pyelo-ureteritis cystica. Air bubbles, accidentally injected in retrograde pyelography, may be a source of speculative diagnosis. Tuberculous pyelo-ureteritis may be recognized by the presence of numerous and complicated changes depending upon the degree of involvement. Blood clots may be responsible for lucent defects, but these are relatively large and are usually irregular in shape. Cellular debris, nonopaque calculi, and varicose ureteral veins, as well as tumors of the renal pelvis and ureter must be considered in the differential diagnosis.—*A. Ralph Watson, M.D.*

SKELETAL SYSTEM

DE REUS, H. D. L'infarctus osseux. (Bone infarct.) *J. belge de radiol.*, 1957, *40*, 20–30. (From: Laboratoire de Radiologie de l'Hôpital Juliana, Apeldoorn, Holland.)

Bone infarcts may be classified as *primary*, when arterial occlusion is the main pathologic disturbance (arteriosclerosis; caisson or other decompression diseases), and *secondary*, in which the interruption of blood supply is only coincidental (fracture; osteomyelitis; bone tumors). The favored location is either or both meta- and epiphyseal, found most often in the proximal humeral and femoral epiphyses, in the femoral condyle, and the humeral, tibial, and femoral metaphyses.

There is at first a subchondral necrosis, followed by resorption of the devitalized segment, and subsequent replacement by new bone, or by fibrous tissue, which may undergo irregular, patchy calcification. When the infarct involves an articular surface, weight-bearing may cause local collapse, with consequently severe arthritic changes of the degenerative type.

The pathogenesis remains obscure in many cases, although beyond middle age, one may always consider the possibility of peripheral stenotic arteriosclerosis (Uehlinger). It is difficult to explain why so few infarcts are seen in severe occlusive vascular disorders of the extremities, and why so many infarcts appear in sickel-cell anemia. Some connection seems to exist between bone infarcts and idiopathic aseptic necrosis (Calvé-Legg-Perthes, Osgood-Schlatter, etc.). Peripheral angiography may help in solving some of the many questions still open in our knowledge of the formation of bone infarcts.

Smaller infarcts cannot be demonstrated on the roentgenogram, particularly when replaced by new bone formation. Even larger infarcts escape detection, because they are often asymptomatic, and routine bone survey is seldom economically justified. When located on articular surfaces, differentiation from an arthritic process is not always possible. In the metaphysis, the roentgenographic appearance resembles a calcified enchondroma, other possibilities being special types of central osteomyelitis, calcified cartilaginous or bone islands, calcified intra-osseous parasites, and even malignant osteoblastic tumor (so far, periosteal reaction has never been described in association with bone infarct, except when superimposed inflammatory process intervenes). The diagnosis is usually easy, but occasionally biopsy may be required for final evaluation.—*E. R. N. Grigg, M.D.*

GRAINGER, RONALD G., and LAWS, JOHN W. Paget's disease—active or quiescent? *Brit. J. Radiol.*, March, 1957, *30*, 120–124. (From: X-Ray Department, St. Thomas' Hospital, London, S.E. 1, and Radiodiagnostic Department, Hammersmith Hospital, London, W. 12, England.)

It is generally believed that the bone changes in most patients with Paget's disease are slowly progressive; however, in some cases, the roentgen changes remain static for many years. It seems probable that the disease process fluctuates considerably in the degree of activity.

The authors carried out a two year survey on 20 patients with Paget's disease and found that 8 had progressive roentgen changes. Of these patients, 3 had osteoporosis circumscripta, 2 had pathologic fractures through the osteoporotic demarcation zones, 1 had pathologic compression fractures of the porotic diseased vertebrae and 2 patients had incomplete or pseudo fractures. The common roentgen finding in all these active cases was local osteoporosis, which was always the initial feature when normal bone became involved. This confirms the observation that the initial lesion in Paget's disease is bone destruction, the cause of which is entirely obscured. The resulting weakness of the involved bones renders them less resistant to stress and strain and leads to stimulation of the osetoblasts and overproduction of bone. Sosman suggested in 1927 that osteoporosis circumscripta was the absorptive or destructive phase of Paget's disease with the productive phase held in abeyance. Since osteoblastic activity is stimulated by physical stresses and strains on weakened bone, the relative absence of such stresses on the calvarium will result in little osteoblastic stimulation and therefore little new bone formation. Circumscribed osteoporosis is found less commonly in the other bones of the skeleton because the greater stresses and strains to which they are subjected result in early new bone formation.

Illustrations are included to show the progress of

the disease and charts are presented summarizing the cases in the series.

The authors conclude that their demonstration of local osteoporosis as the essential and earliest roentgen feature in Paget's disease is in accordance with the findings of other workers, indicating that the initial lesion is a local osteoporosis with consequent weakening of the bone and liability to pathologic fracture.—*Robert D. Moreton, M.D.*

Bream, Charles A., and Sprunt, William H., III. An unusual cystic lesion of bone, limited to the pelvis and lower extremities; osteogenesis imperfecta cystica? *Radiology*, Feb., 1957, *68*, 179–184. (Address: C. A. Bream, School of Medicine, University of North Carolina, Chapel Hill, N. C.)

The authors present a case report of an unusual cystic bone lesion occurring in a young Negro male. Other major abnormalities in several other systems of the body were also present and complicated the picture. No definite relationship could be demonstrated between these abnormalities and the cystic lesions. Roentgenograms taken at an interval of four years were studied as were 2 biopsies.

All the bones of the feet showed cystic changes completely replacing the normal trabecular pattern and marked cortical thinning was present. Similar abnormalities were evident in the diaphyseal ends of both tibiae and fibulae. The cystic changes in the femurs were accompanied by marked diaphyseal widening, within which could be seen the ghost-like shadows of normal appearing femoral shafts. The diaphyseal cortex in the femurs was extremely thin and in some areas was absent. The cystic changes in the pelvis were similar to those in the feet. Demineralization was present only in the spine. All the other bones were normal. The only change seen in the 2 sets of roentgenograms was in the distal end of the left tibia and this was thought to be the result of a previous biopsy.

The bone diseases considered in the differential diagnosis and ruled out included: osteitis fibrosa cystica, osteitis fibrosa polyostotica, lymphangiectasis, osteomyelitis, malignant neoplasm, hemangioendothelioma of bone, osteogenesis imperfecta cystica and lipoid reticulosis of bone. The final diagnosis was an "undiagnosed abnormality of bone." Several roentgenograms are reproduced illustrating the lesions.—*Donald N. Dysart, M.D.*

O'Connor, Sylvester J., and Ivanoff, John C. Infantile cortical hyperostosis. *Ann. Surg.*, April, 1957, *145*, 573–579. (From: Department of Surgery, Section of Orthopedics, University of Michigan, Ann Arbor, Mich.)

Infantile cortical hyperostosis may be a not uncommon syndrome. Occurring in infancy, its cause is variable—very frequently demonstrating pallor, painful pseudoparalysis, pseudotumor and pleurisy. Certain bones characteristically show roentgenographic evidence of subperiosteal new bone deposition of extremely variable degree which waxes, then wanes in a process of eventual regression to normal. At least one fatal case has, however, been reported. Constitutional symptoms and soft tissue findings precede bony alteration. This has led to the logical supposition that the initial disturbance may be in muscle or in blood vessels which in some way stimulate periosteal growth.

The authors report a case of scapular cortical hyperostosis in a two-month old infant.—*C. Peter Truog, M.D.*

Meaney, Thomas F., and Hays, Robert A. Roentgen manifestations of psoriatic arthritis. *Radiology*, March, 1957, *68*, 403–407. (Address: T. F. Meaney, 2020 East 93 St., Cleveland 6, Ohio.)

Psoriatic arthritis is commonly understood as an arthritis affecting patients with longstanding psoriasis. The joint manifestations usually involve the hands and most often are associated with psoriatic changes in the nails.

Fifteen patients with psoriasis and arthritis, in whom bone and joint abnormalities were demonstrated by roentgenography of the hands, form the basis of this study. Roentgen findings typical of rheumatoid arthritis were present in 11 patients. The roentgenograms showed generalized demineralization of bone, narrowing of the joint spaces, some erosion about the articular surfaces, and soft-tissue swelling about the involved joints—usually the proximal interphalangeal joints. Four patients showed changes atypical for rheumatoid arthritis. Bone density was normal in these and there were varying degrees of articular destruction involving the terminal interphalangeal joints with some hypertrophic changes also often present.

It is the authors' opinion that these findings in this second group represent a distinct type of arthritis for which the appropriate term is psoriatic arthritis.—*Donald N. Dysart, M.D.*

Gibson, H. J. Ankylosing spondylitis: Aetiology and pathology. *J. Fac. Radiologists*, Jan., 1957, *8*, 193–200. (From: Area Pathologist, Bath, England.)

Ankylosing spondylitis is a disease of unknown cause. Various workers have shown that the disease has a strong familial tendency. It occurs about ten times more commonly in men than in women. Its relation to rheumatoid arthritis is not clearly defined and new evidence appears to be equally divided on the question of the identity of these two diseases. Histopathologically the essential features appear to be inflammatory destruction followed by excessive

bone formation on biopsies taken from tips of spinous processes, while biopsies from the manubriosternal and sacro-iliac joints indicate change from fibrocartilage, to fibrous tissue, to chondroid, to bone, with no truly inflammatory phase. In the synchondroses, the disease resembles, in many respects, a speeding up of the normal aging process. In posterior spinal and facet joints, adhesions rapidly form following a villous synovitis. Then chondroid metaplasia in the fibrous adhesions is followed by ossification and bony ankylosis. In the intervertebral disks, ossification of peripheral fibers of the annulus fibrosus occurs, spreading from the margin of the epiphysial ring of the vertebral body on either side and meeting in the middle. This results in "beaking" and then the "bamboo" spine.

In the peripheral joints in ankylosing spondylitis, the histologic appearance of the synovial membrane may be identical with that of rheumatoid arthritis. The real difference between rheumatoid arthritis and ankylosing spondylitis in the peripheral diarthrodial joints is in the tendency in ankylosing spondylitis toward ankylosis.

In rheumatoid arthritis, the serum in a fairly high proportion of cases agglutinates the hemolytic streptococcus. This antibody is lacking in ankylosing spondylitis. Recently a further interesting antibody has been described in the Rose test. Serum from a majority of cases of rheumatoid arthritis and disseminated lupus agglutinates sensitized sheep red cells, that is, sheep red cells treated with an antibody prepared against them by immunizing another species such as a rabbit. It is quite empirical and the test is usually negative in ankylosing spondylitis.

Gold therapy is effective in rheumatoid arthritis but not in ankylosing spondylitis. On the other hand, radiation therapy appears to be of real value in ankylosing spondylitis, but it has little or no effect in rheumatoid arthritis.

The author believes that these 2 diseases are of the same family, but are no more related than acute rheumatism and polyarteritis nodosa or rheumatoid arthritis and scleroderma. The association of both diseases in the same patient may indicate relationship but not identity.—*Samuel G. Henderson, M.D.*

STOLL, BASIL A. Ankylosing spondylitis: Its hormonal background in relation to x-ray therapy. *J. Fac. Radiologists*, Jan., 1957, *8*, 201–214. (From: Peter MacCallum Clinic, Melbourne, Australia.)

In view of the remarkable male predominance in ankylosing spondylitis and its earliest manifestations appearing at the age of maximum sexual activity, there has been considerable speculation as to the relation of the disease to hormone dysfunction. Roentgen therapy is practically diagnostic in its ability to relieve the symptoms of the disease. If it be accepted that roentgen irradiation stimulates the secretion of its hormone by the adrenal cortex, perhaps the beneficial effect of roentgen therapy in ankylosing spondylitis is exerted indirectly by stimulation of the adrenal cortex, rather than directly by local action.

Etiologically it is noted that: (1) The sex distribution averages about 10 males to 1 female; (2) the onset of symptoms is usually in young adult life; (3) those subjected to mental stress are more particularly affected; (4) there is a familial history of spondylitis in about 10 per cent of cases; (5) in females the disease is usually less rapidly progressive and may abort spontaneously before ankylosis develops; (6) iritis is noted in about 8 per cent of cases; (7) ankylosing spondylitis is associated with the asthenic male type; and (8) there is a high level of 17-ketosteroid excretion in many cases of ankylosing spondylitis, with fall in level subsequent to clinical benefit derived from roentgen therapy.

Ankylosing spondylitis responds to cortisone, but there is no lasting effect, unlike from roentgen therapy. There are several reports that intramuscular administration of 20 mg. stilbestrol daily gives a definite and lasting improvement in the flexibility of the spine, together with relief of pain, but in males mastitis and impotence often result.

There are 5 techniques of roentgen therapy which are still in general use. These include: (1) Localized low-dose technique; (2) whole spine low-dose technique; (3) wide-field therapy; (4) localized protracted low-dose technique; and (5) whole spine high-dose technique.

There is a remarkable diversity in the dose of roentgen rays given by different radiation therapists in treating this disease with, however, remarkably uniform results. There appear to be 3 possible modes of action of roentgen therapy in these cases. These are: (1) Local action on the involved joints; (2) indirect effect via the autonomic system; and (3) indirect effect via the adrenal cortex.

Since the introduction of cortisone in the treatment of rheumatoid arthritis and spondylitis, the author has felt that the action of irradiation in treatment of ankylosing spondylitis may be to increase the level of cortisone in the blood, so that the patient is treated by endogenous endocrine therapy. Most English and American authors do not accept this mode of action of roentgen therapy. Experimental observations confirm that irradiation of various parts of the body, particularly of the adrenal gland, leads to a stress reaction with increased activity of the adrenal cortex. The author therefore suggests that the action of roentgen therapy in ankylosing spondylitis is, in the main, by stimulation of the secretion of the adrenocortical hormone, rather than by a local action upon the involved ligaments and joints. Roentgen therapy of the adrenal glands in 18 subjects, 10 with ankylosing spondylitis and 8 with osteoarthritis of the spine, was carried out. He administered 750 to 900 r in ten to fourteen days over the adrenal glands. Of the patients with ankylosing

spondylitis, 9 had marked to complete relief, and 1 had partial relief, while in the 8 patients with osteoarthritis, 7 had no relief, 1 had some relief of lumbosacral pain. The technique is simple. It is without danger of damage to the ovaries, and is unlikely to lead to any bone marrow changes.—*Samuel G. Henderson, M.D.*

Blood and Lymph System

Poser, Charles M., and Taveras, Juan M. Cerebral angiography in encephalo-trigeminal angiomatosis. *Radiology*, March, 1957, *68*, 327–336. (Address: C. M. Poser, University of Kansas Medical Center, Kansas City 3, Kansas.)

Encephalo-trigeminal angiomatosis consists essentially of a vascular anomaly of the skin of the face, in an area served by the trigeminal nerve, associated with a presumed intracranial vascular anomaly. Clinically, these cases can be divided into 3 categories: Type I: Typical Sturge-Weber encephalo-trigeminal angiomatosis in which there are a port-wine nevus and at least 2 other features of the syndrome, as convulsions, hemiparesis, hemiatrophy or hemihypertrophy, mental retardation, buphthalmos or congenital glaucoma. Type II: The incomplete form in which the skin manifestations are absent, but other classical features of the syndrome are present. Type III: The so-called atypical cases which have some type of facial vascular anomaly (but not the port-wine nevus) and other features of the syndrome.

This report is based on the study of a total of 50 patients with this condition who had cerebral angiography. Fifteen of these were from the authors' institution and the other 35 were collected from the literature. Positive angiograms were obtained in a total of 15 of the 34 typical (clinical Type I) cases and in 4 each of the 8 cases of the incomplete form (Type II) and of the atypical form (Type III). Only 12 patients showed the typical angiographic findings of diffuse areas of homogeneous increase in density due to intracranial venous angioma or telangiectases, and these were most frequently located in the posterior parietal regions.

Other findings consisted of arteriovenous malformations (2 patients), arterial thrombosis (4 patients), anomalies of veins or venous sinuses (5 patients), abnormalities within the territory of the external carotid artery (3 patients), subdural hematoma (1 patient), and cerebral atrophy (6 patients). Intracranial calcification was present on routine skull roentgenograms in 27 of 47 cases where specific mention was made of its presence or absence, and in only 10 of these was cerebral angiography positive. Thirteen of the 20 cases without calcification had positive angiograms. In general, the average age of the patients with positive angiograms was lower in both the group with and without calcification. It was found that increasing age and the presence of intracranial calcification decreased the chances of demonstrating vascular abnormalities by cerebral angiography.

Two cases, in which the authors were able to obtain follow-up studies, showed rapid development of massive Weber-type calcification in the previously demonstrated capillary-venous angioma. From this study the conclusion is drawn that, if an intracranial angioma can be shown, rapid and massive cortical calcification will probably develop.—*Donald N. Dysart, M.D.*

Schmidt, J. Röntgendiagnostische Besonderheiten der Arteria lusoria. (Roentgen diagnostic features of the arteria lusoria.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, Feb., 1957, *86*, 188–192. (From: Medizinische Universitäts-Poliklinik, Erlangen, Germany.)

The term arteria lusoria is used for an ectopic right subclavian artery arising from the aortic arch on the left side as its last branch. The artery passes to the right and cephalad, usually behind the esophagus and causes a pressure deformity of the posterior esophageal wall, sometimes associated with dysphagia.

The author observed, in patients with this congenital malformation, an unusually prominent, high aortic knob, which could not be explained by other pathologic processes. This finding was considered of value particularly in adolescents and young women where the aortic knob is usually small. The pressure defect of the esophagus can be caused by other rare anomalies of the great vessels which can be differentiated by aortography. The diagnosis of ectopic right subclavian artery can be made also by cardiac catheterization from the abnormal course of the catheter introduced through the right artery into the aorta. An ingenious and simple method was devised by Facquet and associates, who introduced a sound filled with mercury into the esophagus, which with the patient supine compressed the vessel against the dorsal spine with a resulting drop in blood pressure in the right arm.

The article contains reproductions of 5 roentgenograms and 13 references.—*Karol E. Matzinger, M.D.*

Steiner, R. E., Sherlock, Sheila, and Turner, M. D. Percutaneous splenic portal venography. *J. Fac. Radiologists*, Jan., 1957, *8*, 158–177. (From: Departments of Radiology and Medicine, Hammersmith Hospital and Postgraduate Medical School of London, London, England.)

This paper is a report of 100 percutaneous transsplenic venographies and a discussion of the technique.

Technique: Premedication:—Papaveretum 20 mc.

and scopolamine 0.3 mg. or sodium amytal 200 mg. and pethidine 100 mg.

Local anesthesia (2 per cent procaine) in adults; general anesthesia in children.

Schonander biplane serial angiographic table; 2 roentgenograms exposed synchronously in lateral and in anteroposterior projections; 10 roentgenograms taken in each plane in seven seconds.

Injection at point of maximum splenic dullness in midaxillary line in eighth or ninth intercostal space, following infiltration with 2 per cent procaine down to splenic capsule.

Needle, 7 cm. long, fitted with stilette and screw adaptor connecting it by polyethylene tubing to injection syringe.

Needle directed slightly upward and backward at an angle of about 20 degrees. Patient asked to hold his breath during introduction of needle, also, while polyethylene tube from syringe is connected to the needle by a pressure-tight screw connection.

In adults, 40 cc. of 70 per cent diodone injected; 10 to 20 cc. in children. Contrast material injected at rate of 5 cc. per second; the first roentgenogram being taken after two-thirds of contrast material has been injected. Injection is completed just before last roentgenogram is taken.

The normal portal venogram: The portal vein is formed by the junction of the superior mesenteric and splenic veins. The inferior mesenteric vein drains into the splenic vein and the portal vein at its origin. In all patients a "pool" of contrast medium is seen in the splenic pulp, the bulk of this disappearing in a few seconds, but persisting in part until the end of the examination. The main splenic vein and occasionally some collateral veins are outlined. The contrast material flows rapidly along the portal vein, filling its branches in the liver, with perfectly even branching and reduction in caliber of the smaller radicles out to the periphery of the liver. On the later roentgenograms there is opacification of the liver sinusoids, production of a "hepatogram." The normal spleen-liver time is two to three seconds.

Venographic appearance in disease: In 56 patients with portal cirrhosis, a normal venogram or an insignificant number of collateral vessels was seen in 15 patients, while multiple collaterals were demonstrated in 32 and mainly one large collateral in 9 patients. Filling of the inferior vena cava was seen in 6 patients, total blocking of portal vein in 4 patients, and partial blocking in 2 others. The liver pattern was normal in 14 patients and abnormal in 20.

In extrahepatic portal vein obstruction, a marked feature of the venographic appearance was the large number of small veins running from the spleen to the diaphragm and the posterior abdominal wall. The splenic venogram is particularly useful in differentiating extrahepatic portal obstruction from intrahepatic obstruction and may be of value as an emergency procedure in the management of patients requiring surgery to control bleeding from esophageal varices.

If the portal venous sytem is obstructed in the liver (cirrhosis) or from occlusion of the splenic or portal veins, a collateral circulation develops between the portal and systemic venous systems. Anastomoses may occur through a large number of channels throughout the abdomen and thorax.

After portacaval anastomosis, splenic venography can be used to demonstrate the condition of the portacaval shunt and may give a guide to the prognosis with regard to future hemorrhage. Where the anastomosis is functioning satisfactorily, all the contrast medium will be carried into the inferior vena cava and no portal collaterals will be shown.

Indications for trans-splenic venography: (1) Assessment of patients with portal hypertension and gastrointestinal hemorrhage; (2) investigation of portacaval shunts, particularly to determine if the shunt is patent or occluded; (3) diagnosis of extrahepatic portal vein obstruction; (4) unexplained splenomegaly; (5) obscure chronic neuropsychiatric disorders in the presence of portal cirrhosis; and (6) diagnosis of neoplasms involving the splenic or portal vein.

Contraindications: (1) Deep jaundice with or without normal prothrombin time; (2) a one-stage prothrombin time of more than fifteen seconds with platelet count less than 100,000 per cubic millimeter; and (3) ascites (removal of fluid necessary before the investigation).

Complications: There was slight intraperitoneal hemorrhage in 2 patients.

Splenic venography is a more satisfactory method of demonstrating esophageal vessels than barium-swallow examination. Esophageal vessels were shown in 76 patients by venography and in 66 by barium swallow. In only 2 patients were varices shown on barium swallow and not on venography, while in 10, venography demonstrated veins which were not seen on barium examination.—*Samuel G. Henderson, M.D.*